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(54) Title: ADVANCED INDOLINONE BASED PROTEIN KINASE INHIBITORS

(57) Abstract: Hydroxy carboxy pyrrolyl-indolinone derivatives have enhanced and unexpected drug properties as inhibitors of protein kinases and are useful in treating disorders related to abnormal protein kinase activities such as cancer.

ADBVANCED INDOLINONE BASED PROTEIN KINASE INHIBITORS

Description

Field of Invention:

The invention relates to protein kinase inhibitors and to their use in treating disorders related to abnormal protein kinase activities such as cancer and inflammation. More particularly, the invention relates to hydroxyl carboxy pyrrolyl-indolinone derivatives and their pharmaceutically acceptable salts employable as protein kinase inhibitors.

Background:

Protein kinases are enzymes that catalyze the phosphorylation of hydroxyl groups of tyrosine, serine, and threonine residues of proteins. Many aspects of cell life (for example, cell growth, differentiation, proliferation, cell cycle and survival) depend on protein kinase activities. Furthermore, abnormal protein kinase activity has been related to a host of disorders such as cancer and inflammation. Therefore, considerable effort has been directed to identifying ways to modulate protein kinase activities. In particular, many attempts have been made to identify small molecules that act as protein kinase inhibitors.

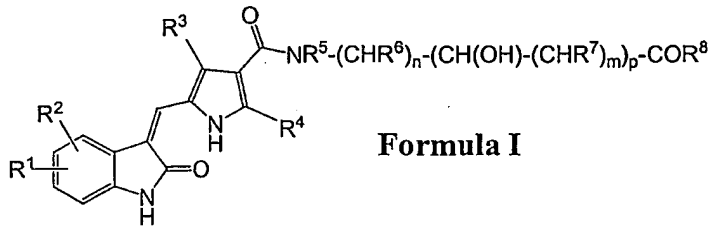
Several pyrrolyl-indolinone derivatives have demonstrated excellent activity as inhibitors of protein kinases (Larid et al. FASEB J. 16, 681, 2002; Smolich et al. Blood, 97, 1413, 2001; Mendel et al. Clinic Cancer Res. 9, 327, 2003; Sun et al. J. Med. Chem. 46, 1116, 2003). The clinical utility of these compounds has been promising, but has been partially compromised due to the relatively poor aqueous solubility and/or other drug properties. What is needed is a class of modified pyrrolyl-indolinone derivatives having both inhibitory activity and enhanced drug properties.

Summary:

The invention is directed to hydroxy carboxy pyrrolyl-indolinone derivatives and to their use as inhibitors of protein kinases. It is disclosed herein that hydroxy

carboxy pyrrolyl-indolinone derivatives have enhanced and unexpected drug properties that advantageously distinguish this class of compounds over known pyrrolyl-indolinone derivatives having protein kinase inhibition activity. It is also disclosed herein that hydroxy carboxy pyrrolyl-indolinone derivatives are useful in treating disorders related to abnormal protein kinase activities such as cancer.

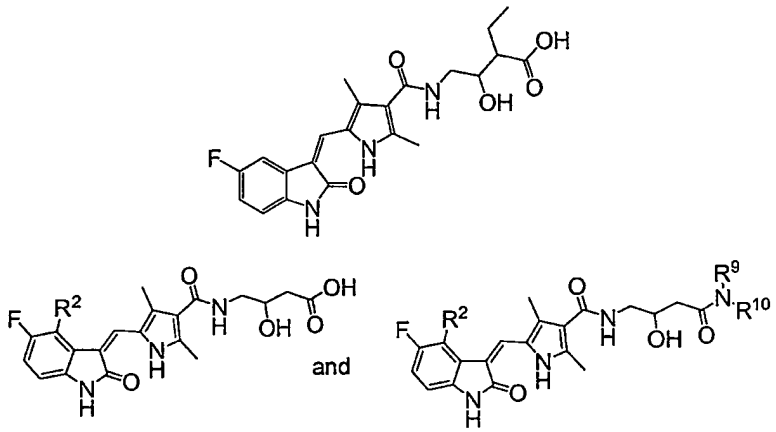
One aspect of the invention is directed to a compound represented by Formula (I):



Formula I

In Formula I, R^1 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, amino, (C1-C6) alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted (C6-C10) aryl; R^2 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, (C2-C8) alkoxyalkyl, amino, (C1-C6) alkylamino, (C6-C10) arylamino; R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C6-C10) aryl, (C5-C10) heteroaryl, and amide; R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen and (C1-C6) alkyl; each R^7 is independently selected from the group consisting of hydrogen, (C1-C6) alkyl and hydroxyl; R^8 is selected from the group consisting of hydroxy, (C1-C6) O-alkyl, (C3-C8) O-cycloalkyl, and NR^9R^{10}; where R^9 and R^{10} are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^9 and R^{10} together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; and **n** and **m** are independently 0, 1, 2, or 3; p is 1, 2, or 3. Alternatively, this aspect of the invention may also be directed to

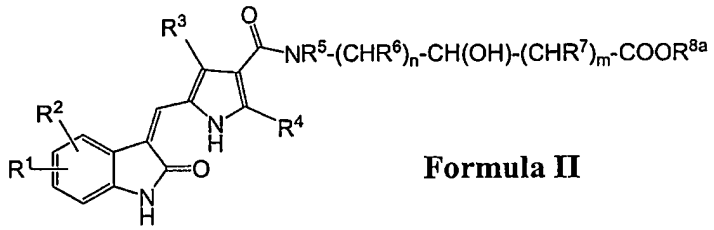
a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug of compounds represented by Formula (I). Key features of this aspect of the invention include the hydroxyl moiety or moieties between R^6 and R^7 and the carboxy moiety between R^7 and R^8. It is disclosed herein that these key features enhance the drug properties of the attached pyrrolyl-indolinone pharmacophore. Preferred species of this aspect of the invention include compounds represented by the following structures:



In the above structures, R^2 is selected from the group consisting of hydrogen and fluoro.

As illustrated above, this first aspect of the invention may be divided into two categories. The first category includes acids and esters; the second category includes amides.

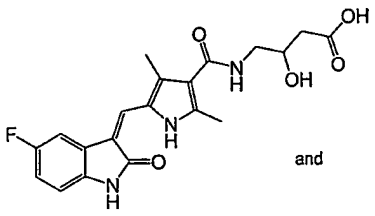
One preferred embodiment of this first category may be represented by Formula (II):



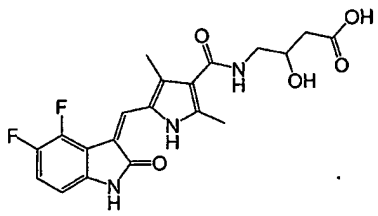
Formula II

In Formula II, R^{8a} is selected from the group consisting of hydrogen, (C1-C6) alkyl, and (C3-C8) cycloalkyl. Within preferred species of this embodiment, R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro; R^3

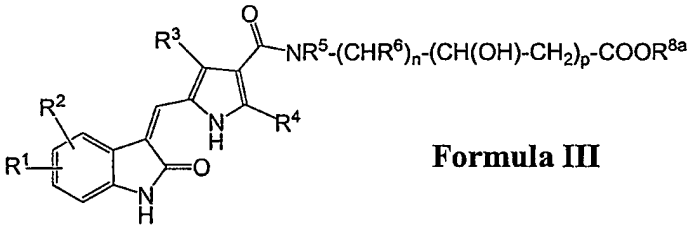
and R^4 are methyl; R^5, R^6, R^7 and R^{8a} are hydrogen; and **n** and **m** are independently 0, 1, or 2. Preferred species include compounds represented by the following structures:



and

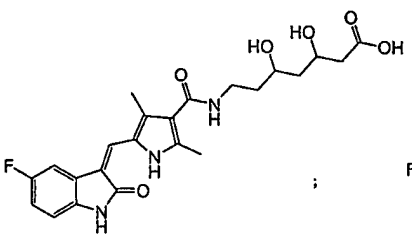


Another preferred embodiment of this first category may be represented by Formula (**III**):



Formula III

In Formula III, R^{8a} is selected from the group consisting of hydrogen, (C1-C6) alkyl, and (C3-C8) cycloalkyl. Within preferred species of this embodiment, R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro; R^3 and R^4 are methyl; R^5, R^6, and R^{8a} are hydrogen; and **n** and **p** are independently 1, or 2. Preferred species of this embodiment include compounds represented by the following structures:



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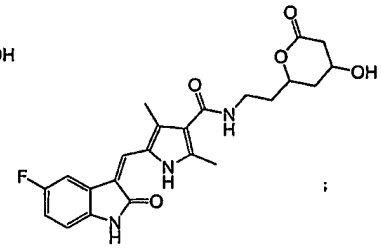

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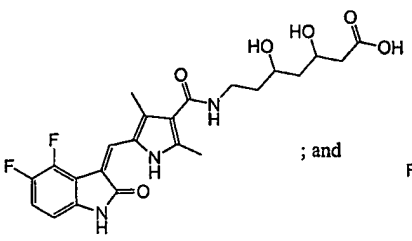
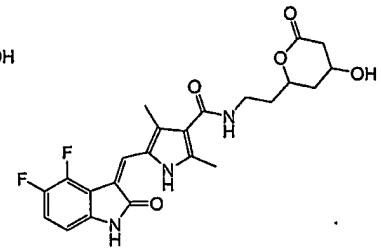
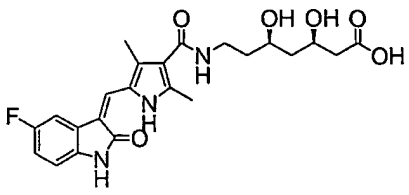


; and



Preferred enantiomeric species of this embodiment of the invention include compounds represented by the following structures:



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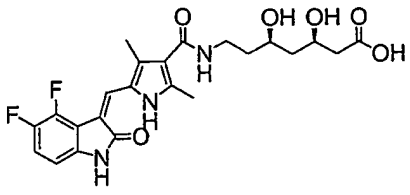
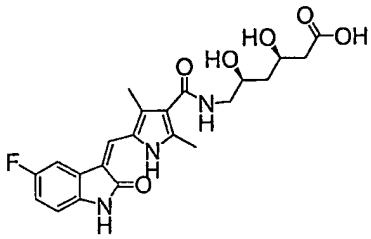
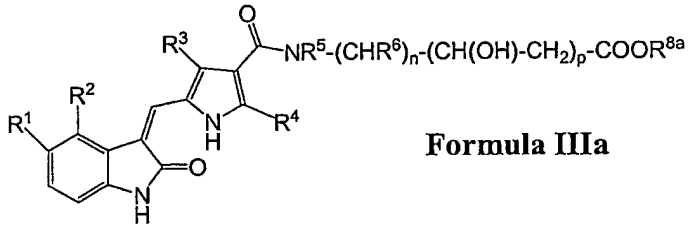


; and



.

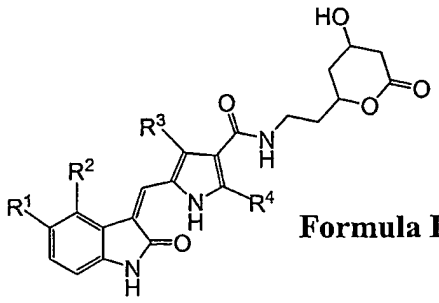
Another preferred embodiment of this first category may be represented by Formula (**IIIa**):



Formula IIIa

In Formula IIIa, R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro; R^3 and R^4 are methyl; R^5, R^6, and R^{8a} are hydrogen; and **n** and **p** are 2. Within this embodiment, each species may exist either as the acid or as the cyclic lactone and they may co-exist in solution or *in vivo*. Furthermore, in the above examples the stereochemistry at the carbon atom carrying a hydroxyl group is either *RS*, *R*, or *S*. The preferred stereochemistry is *R*.

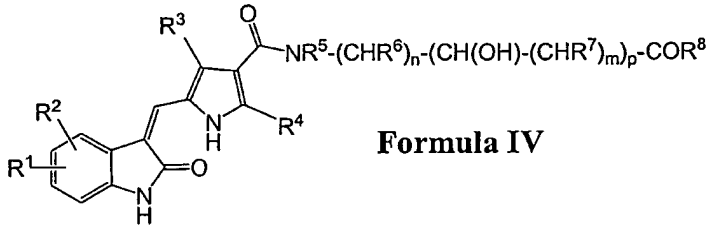
An alternative of the above preferred embodiment of this first category may be represented by Formula (**IIIb**):



Formula IIIb

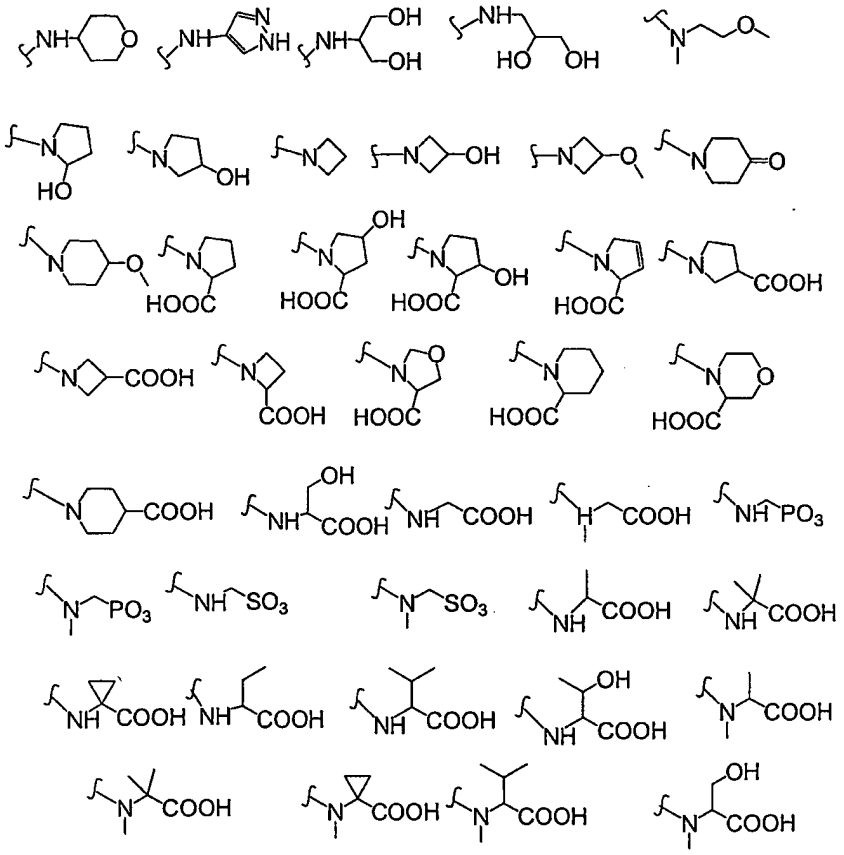
In Formula IIIb, R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro; and R^3 and R^4 are methyl.

The second category of the first aspect of the invention is embodied by a compound, salt, tautomer, or prodrug according to claim 1 represented by Formula (**IV**):

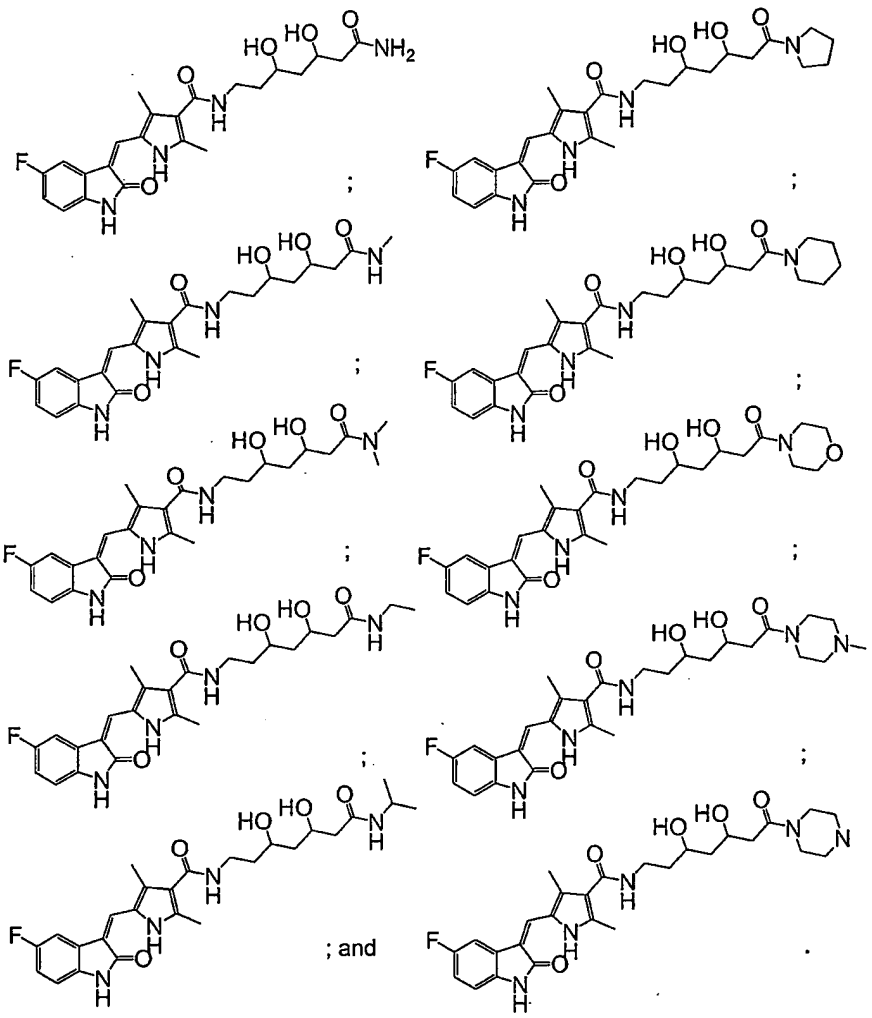


Formula IV

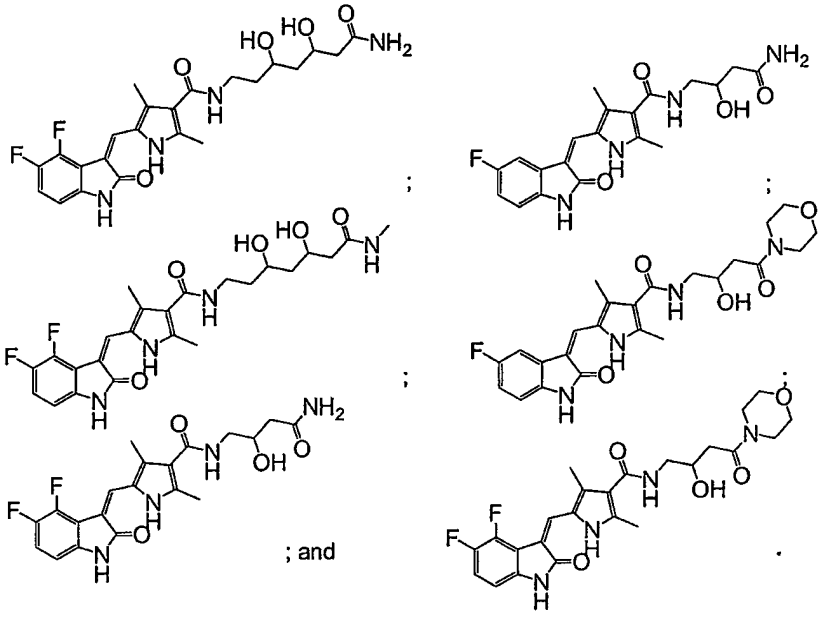
wherein R^8 is NR^9R^{10}. In preferred embodiments of this aspect of the invention, R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, cyano; R^3, R^4, R^5 and R^6 are independently hydrogen or (C1-C6))alkyl; R^7 is hydrogen, or hydroxyl; **n**, and **p** are independently 1, or 2; **m** is 0 or 1; and R^9 and R^{10} are selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^9 and R^{10} together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids. Preferred examples of R^9 and R^{10} include the following radicals and diradicals:



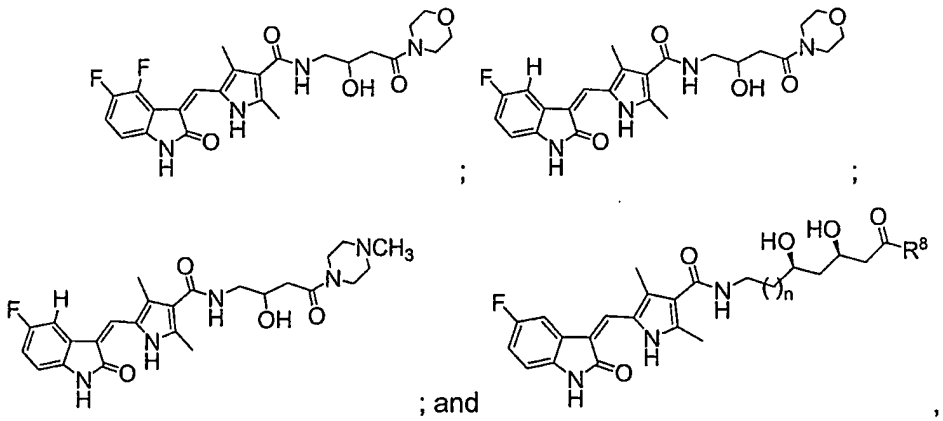
Preferred species of this embodiment may be selected from the group represented by the following structures:



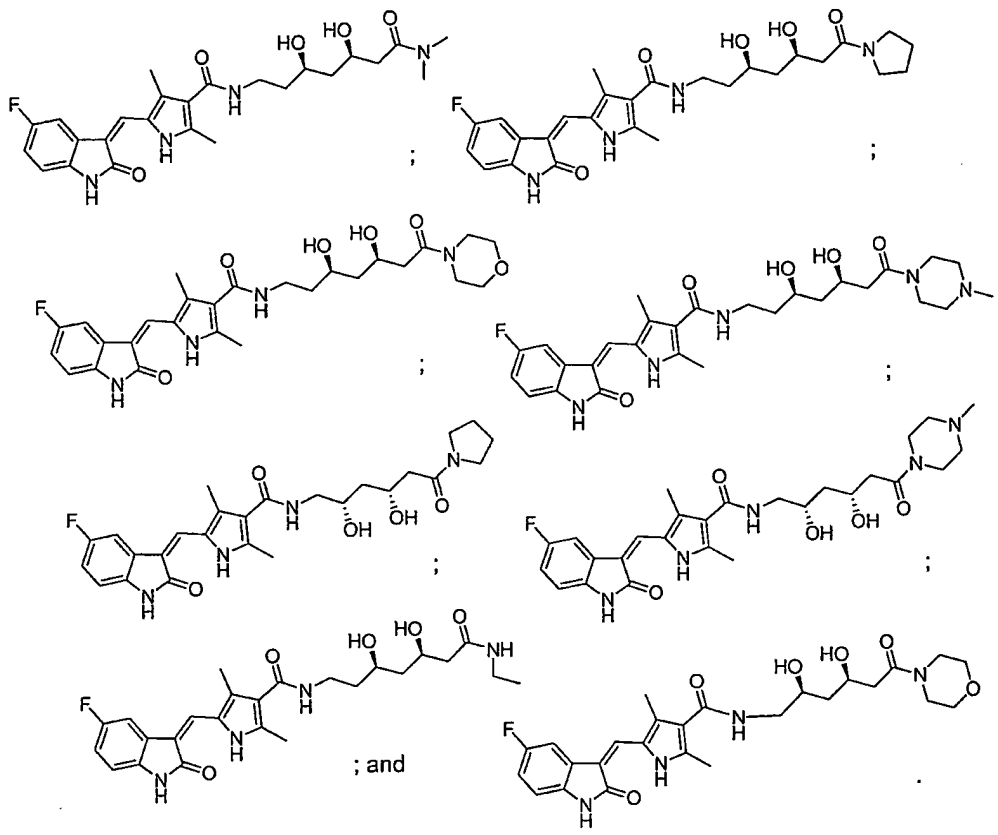
Further preferred species of this embodiment of the invention may be selected from the group represented by the following structures:



Further preferred species of this embodiment of the invention may be selected from the group represented by the following structures:

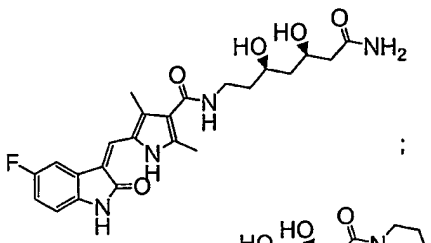


wherein n is 0, 1, or 2. Further preferred species of this embodiment of the invention may be selected from the group represented by the following structures:



; and

Further preferred species of this embodiment of the invention may be selected from the group represented by the following structures: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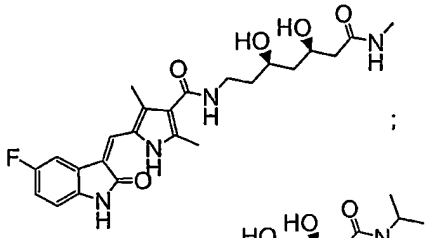
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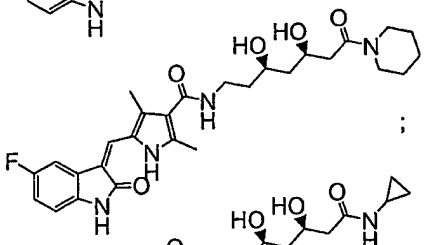
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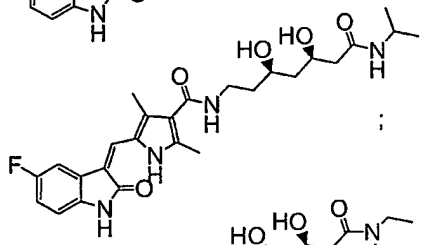
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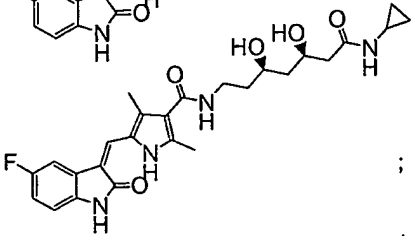
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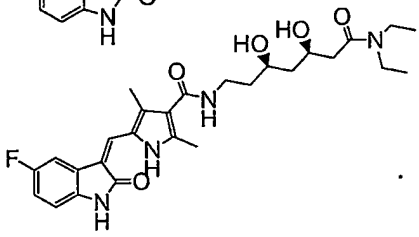
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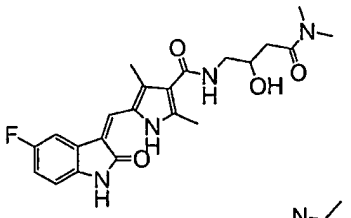
Further preferred species of this embodiment of the invention may be selected from the group represented by the following structures: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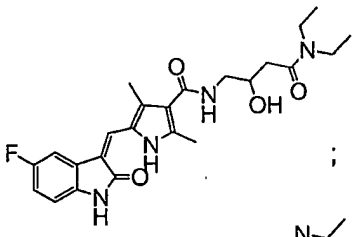
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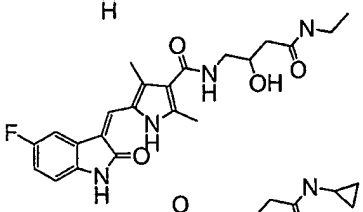
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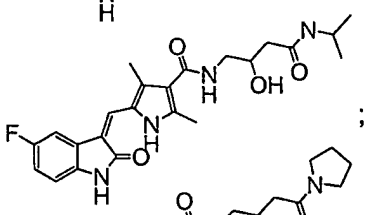
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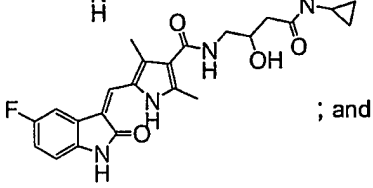
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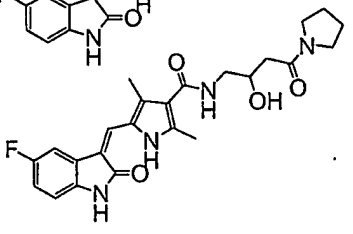
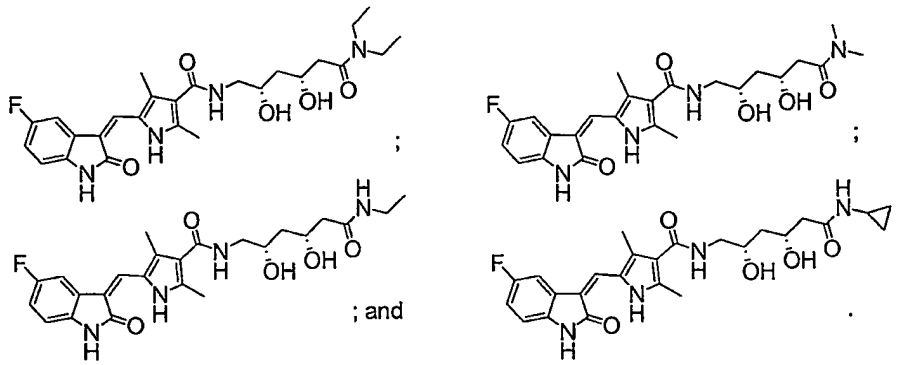
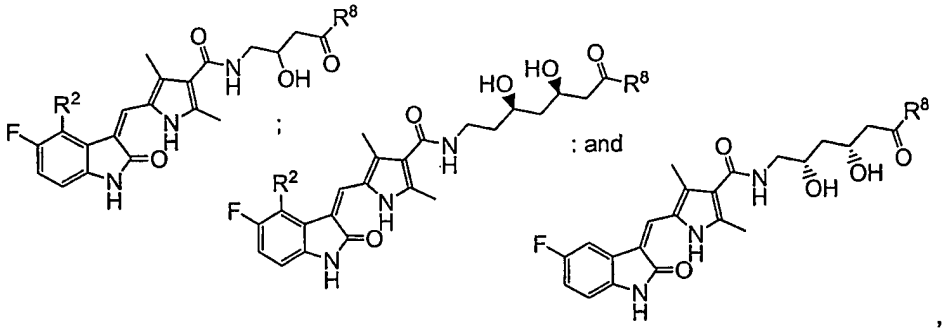

.

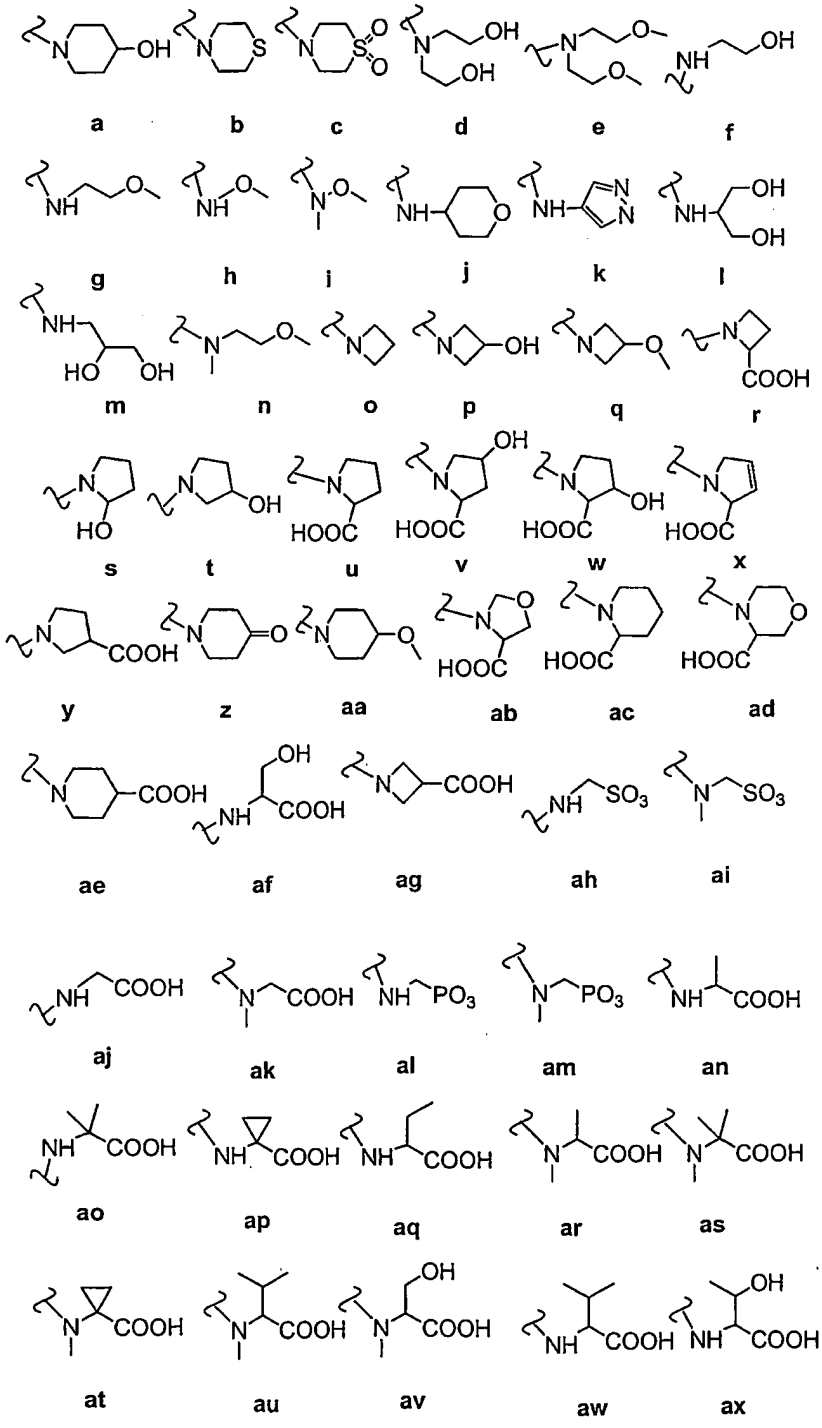
Further preferred species of this embodiment of the invention may be selected from the group represented by the following structures:



Further preferred species of this embodiment of the invention may be selected from the group represented by the following structures:



wherein R^2 is selected from the group consisting of hydrogen and fluoro; and R^8 is selected from the group consisting of radicals represented by the following structures: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Provisios may apply to any of the above categories or embodiments wherein any one or more of the other above described embodiments or species may be excluded from such categories or embodiments.

Another aspect of the invention is directed to a method for the modulation of the catalytic activity of a protein kinase with a compound or salt of the first aspect of the invention. In a preferred mode, the protein kinase is selected from the group consisting of VEGF receptors and PDGF receptors.

Utility:

The present invention provides compounds capable of regulating and/or modulating protein kinase activities of, but not limited to, VEGFR and/or PDGFR. Thus, the present invention provides a therapeutic approach to the treatment of disorders related to the abnormal functioning of these kinases. Such disorders include, but not limited to, solid tumors such as glioblastoma, melanoma, and Kaposi's sarcoma, and ovarian, lung, prostate, pancreatic, colon and epidermoid carcinoma. In addition, VEGFR/PDGFR inhibitors may also be used in the treatment of restenosis and diabetic retinopathy.

Furthermore, this invention relates to the inhibition of vasculogenesis and angiogenesis by receptor-mediated pathways, including the pathways comprising VEGF receptors, and/or PDGF receptors. Thus the present invention provides therapeutic approaches to the treatment of cancer and other diseases which involve the uncontrolled formation of blood vessels.

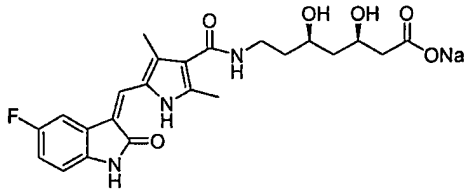
Synthesis of Compounds:

The compounds of this invention can be synthesized by following the published general procedures (e.g. Sun et al., 2003, J. Med. Chem., 46:1116-119). But the following intermediates are specific to compounds of this invention and may be used in place of their respective counterparts in the above-mentioned general procedure: 4,5-difluoro-oxindole; (4*R*,6*R*)-*t*-butyl-6-

(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate; *t*-Butyl(3*R*,5*S*)-6-hydroxy-3,5-O-isopropylidene-3,5-dihydroxyhexanoate, and 4-amino-3-hydroxy-butanic acid. These intermediates may be purchased from commercial sources (e.g. Fisher Scientific, Fairlawn, New Jersey, or Kaneka Corp., Japan). Another variation from the above-mentioned general procedure is that in the synthesis of **1**/**1a** and **2**/**2a** using (4*R*,6*R*)-*t*-butyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, the protecting groups need to be removed from the final product. Yet another variation from the above-mentioned general procedure is that in the synthesis of **3** and **4** using 4-amino-3-hydroxy-butanic acid, the acid needs to be protected before amidation and the protection group needs to be removed from the final product. These variations from the above-mentioned general procedure can be understood and carried out by those skilled in the art. Thus, the compounds of the present invention can be synthesized by those skilled in the art.

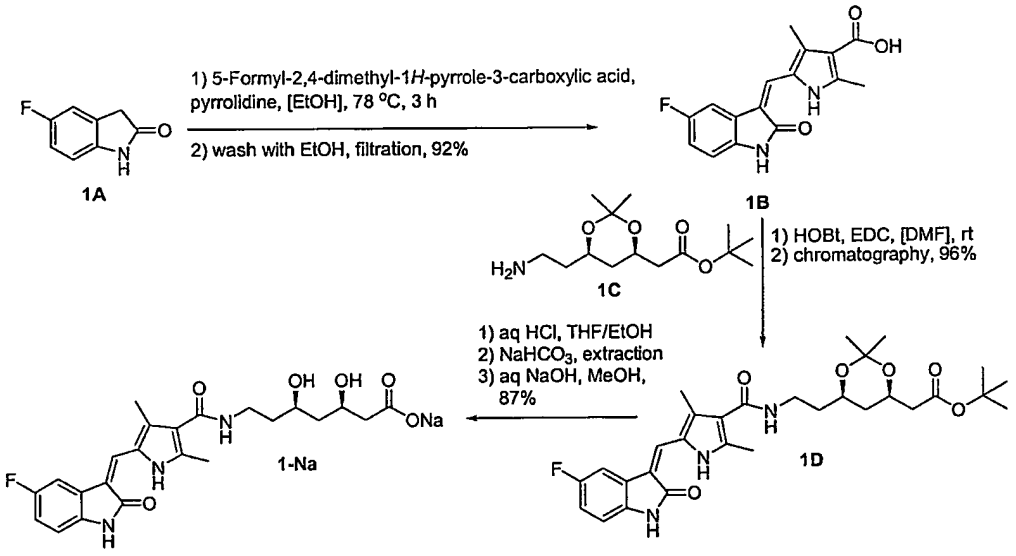
The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

Example 1: (3*R*,5*R*)-7-{[5-(5-Fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carbonyl]-amino}-3,5-dihydroxyheptanoic acid, sodium salt



The synthesis of the title compound is summarized in Scheme 1. In the first step, 5-fluoro-1,3-dihydroindol-2-one (**1A**, purchased from Combi-Blocks, Inc.) was condensed with 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid in refluxing ethanol under the influence of catalytic amounts of pyrrolidine in

analogy to the literature-known preparation of similar compounds (Li Sun, Chris Liang, Sheri Shirazian, Yong Zhou, Todd Miller, Jean Cui, Juri Y. Fukuda, Ji-Yu Chu, Asaad Nematalla, Xueyan Wang, Hui Chen, Anand Sistla, Tony C. Luu, Flora Tang, James Wei, and Cho Tang. Discovery of 5-[5-Fluoro-2-oxo-1,2- dihydroindol-(3Z)-ylidenemethyl]-2,4- dimethyl-1*H*-pyrrole-3-carboxylic Acid (2-Diethylaminoethyl)amide, a Novel Tyrosine Kinase Inhibitor Targeting Vascular Endothelial and Platelet-Derived Growth Factor Receptor Tyrosine Kinase. *J. Med. Chem.* **2003**, *46*, 1116 – 1119) to give pyrrole carboxylic acid **1B** in 92 % yield.

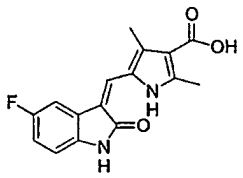


Scheme 1: Synthesis of **1-Na**.

Amide coupling between carboxylic acid **1B** and amine **1C** (obtained from Acros) was affected by treatment with hydroxybenzotriazole, 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride, and triethylamine in DMF to afford **1D**, after chromatographic purification, in 96% yield. Removal of the acetonide and *tert*-butyl ester protective groups was then conducted in a stepwise fashion (H. Jendralla, E. Granzer, B. Von Kerekjarto, R. Krause, U. Schacht, E. Baader, W. Bartmann, G. Beck, A. Bergmann, and et al. Synthesis and biological activity of new HMG-CoA reductase inhibitors. 3. Lactones of 6-phenoxy-3,5-dihydroxyhexanoic acids. *J. Med. Chem.* **1991**, *34*,

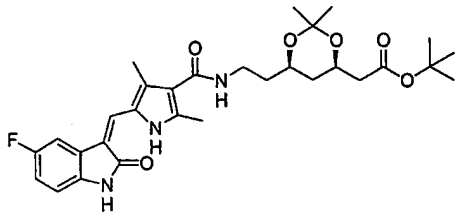
2962 – 2983). First, the acetonide protection in **1D** was removed by treatment with aqueous HCl in a mixture of THF and ethanol to give an intermediary ester diol (not shown), which was isolated by extraction after neutralization of the reaction mixture with sodium bicarbonate. This intermediate was then treated with aqueous NaOH (1 equiv) in methanol to furnish the title compound: **(3*R*,5*R*)-7-{[5-(5-Fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carbonyl]-amino}-3,5-dihydroxyheptanoic acid, sodium salt** (87% yield over both steps) after concentration of the reaction mixture as a yellow solid.

Preparation of 1B: 5-(5-Fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid.



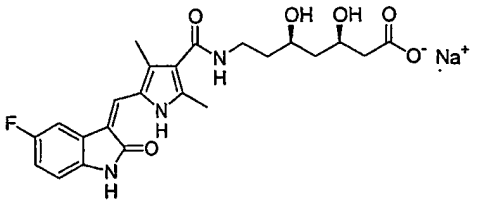
A mixture of 5-fluoro-1,3-dihydroindol-2-one (0.81 g, 5.1 mmol), 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (0.98 g, 5.35 mmol), pyrrolidine (6 drops) and absolute ethanol (15 mL) was heated to reflux for 3 hours. The mixture was cooled to room temperature and the solids were collected by filtration. The solids were stirred with ethanol (14 mL) at 72 °C for 30 minutes. The mixture was cooled to room temperature. The solids were collected by filtration, washed with ethanol (3 mL), dried under vacuum at 54 °C overnight to give 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (1.4 g, 91.5% yield) as an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.19 (br s, 1H), 10.95 (s, 1H), 7.90-7.70 (m, 2H), 7.00-6.80 (m, 2H), 2.54 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.4, 165.7, 159.6, 156.5, 140.7, 134.6, 133.3, 128.9, 126.8, 125.9, 124.7, 115.5, 114.2, 110.9, 110.0, 106.3, 105.9, 14.6, 11.6.

Preparation of 1D: (4*R*,6*R*)-[6-(2-{[5-(Fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carbonyl]-amino}-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester.



To a stirred solution of 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (1.3 g, 4.33 mmol) in dimethylformamide (11.6 mL) at room temperature were added 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (1.25 g, 6.39 mmol), hydroxybenzotriazole (0.88 g, 6.39 mmol), triethylamine (1.3 mL, 9.34 mmol), and (4*R*,6*R*)-[6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester (1.38 g, 4.87 mmol). The reaction mixture was stirred at room temperature for 30 h, then filtered through a silica gel pad and washed with ethyl acetate (100 mL). The filtrate was concentrated and the residue was diluted with water (20 mL), saturated sodium bicarbonate solution (10 mL) and 10 N sodium hydroxide solution (5 mL). The mixture was extracted with a mixture of methylene chloride/methanol (9/1, 2 × 50 mL). The combined organic layers were concentrated to dryness. The residue was triturated with heptane/diethyl ether (3/1, 60 mL). The solids were collected by filtration and dried under vacuum at 34 °C overnight to obtain (4*R*,6*R*)-[6-(2-{[5-(fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carbonyl]-amino}-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester (2.3 g, 95.6%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.05 (br s, 1H), 7.94 (d, *J* = 6.9Hz, 1H), 7.85 (s, 1H), 7.14-6.90 (m, 2H), 4.35 (m, 1H), 4.12 (m, 1H), 3.51 (br s, 1H), 3.42 (m, 2H), 2.64 (m, 2H), 2.57 (s, 3H), 2.56 (s, 3H), 2.50-2.30 (m, 2H), 1.76 (m, 3H), 1.54 (s, 9H), 1.41 (s, 3H), 1.24 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.4, 164.4, 159.6, 156.5, 136.2, 134.3, 129.9, 127.1, 126.9, 125.6, 124.7, 120.8, 114.4, 112.3, 112.0, 109.9, 109.8, 105.9, 105.6, 97.9, 79.6, 66.5, 65.9, 42.2, 35.9, 35.8, 35.1, 29.9, 27.7, 19.6, 13.3, 10.5.

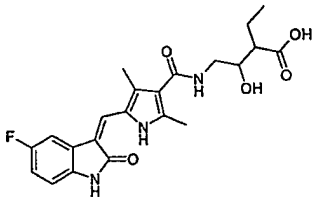
Preparation of 1-Na: (3*R*,5*R*)-7-{[5-(5-Fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carbonyl]-amino}-3,5-dihydroxyheptanoic acid, sodium salt.



Under argon atmosphere and exclusion of light, a solution of (4*R*,6*R*)-[6-(2-{[5-(fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carbonyl]-amino}-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester (1.69 g, 3.04 mmol) in ethanol (15.2 mL), THF (7.6 mL) and 2 N hydrochloric acid (1.7 mL) was stirred at room temperature for 24 hours. The reaction mixture was neutralized with sodium bicarbonate solution (0.256 g $NaHCO_3$ in 5 mL water) to pH 7 and concentrated to remove ethanol and THF. The residue was diluted with water (50 mL) and extracted with a mixture of methyl *tert*-butyl ether/methanol (9/1, 200 mL), and then with methyl *tert*-butyl ether (3 × 50 mL). The combined organic layers were dried over magnesium sulfate and concentrated to dryness to give (3*R*,5*R*)-7-{[5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carbonyl]-amino}-3,5-dihydroxyheptanoic acid *tert*-butyl ester (1.57 g, 3 mmol). This ester (1.56 g, 3.0 mmol) was dissolved in methanol (33.4 mL) and a solution of sodium hydroxide (0.12 g, 3.0 mmol) in deionized water (8.3 mL) was added. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated to dryness. The residue was dissolved in methanol (66 mL) and the mixture was concentrated again. The mixture was triturated with isopropanol (40 mL). The solids were collected by filtration, washed with diethyl ether (100 mL) and dried under vacuum at 34 °C for 3 hours to furnish (3*R*,5*R*)-7-{[5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrole-3-carbonyl]-amino}-3,5-dihydroxyheptanoic acid, sodium salt (1.28 g, 87.4% yield over two steps) as a yellow solid. Mp 256-258 °C (decomposition). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.49 (s, 1H),7.31 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 6.6 Hz, 1H), 4.03 (m,

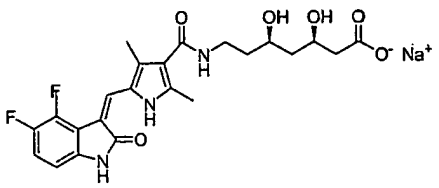
1H), 3.83 (m, 1H), 3.45 (m, 1H), 3.37 (m, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 2.25 (m, 2H), 1.85-1.40 (m, 4H). ^{13}C NMR (75 MHz, methanol-d_4) δ 180.1, 171.4, 168.4, 161.8, 158.7, 137.7, 135.7, 131.4, 128.6, 128.5, 127.3, 125.2, 121.1, 116.4, 113.6, 113.3, 111.1, 110.9, 106.3, 106.0, 69.1, 68.9, 45.5, 44.9, 37.8, 37.7, 13.4, 10.8.

Example with α-Substituent: 2-Ethyl-4-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-3-hydroxy-butyric acid:



The advanced intermediate 4-Amino-2-ethyl-3-hydroxy-butyric acid ethyl ester can be made following published procedures (e.g. Seebach, Dieter; Chow, Hak-Fun; Jackson, Richard F. W.; Lawson, Kevin; Sutter, Marius A.; et al.; J. Am. Chem. Soc. **1985**, *107*, **18**, 5292-5293. Itoh, Toshiyuki; Takagi, Yumiko; Fujisawa, Tamotsu; Tetrahedron Lett. **1989**, *30*; **29**, 3811-3812). Subsequent amide coupling with **1B** followed by deprotection can afford the title compound.

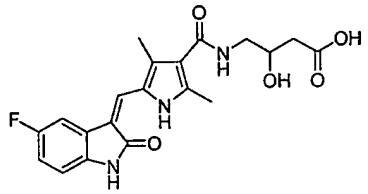
Example 2: (3*R*,5*R*)-7-({5-[4,5-Difluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-3,5-dihydroxy-heptanoic acid, sodium salt



The title compound was prepared following the procedure described in the preparation of Example **1**. In this synthesis, 4,5-difluoro-1,3-dihydroindol-2-

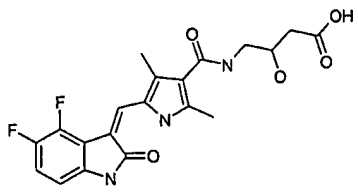
one was used instead of 5-fluoro-1,3-dihydroindol-2-one as in Example **1**. LC-MS: a single peak was observed at 254 nm, MH^+ calcd for the free acid $C_{23}H_{25}F_2N_3O_6$: 478, obtained 478. ^1H NMR (400 MHz, methanol-d_4) δ 7.71 (d, J = 2.4 Hz, 1H), 7.00 (m, 1H), 6.65 (dd, J = 3.2 Hz, J = 8.4 Hz, 1H), 4.13 (m, 1H), 3.93 (m, 1H), 3.56 (m, 1H), 3.45 (m, 1H), 2.48 (s, 3H), 2.39 (s, 3H), 2.34 (m, 2H), 1.84 (m, 1H), 1.69 (m, 3H).

Example 3: 4-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole3-carbonyl}-amino)-3-hydroxy-butyric acid



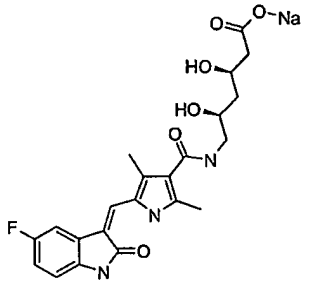
The title compound was prepared following the procedure described in the preparation of Example **1**. In this synthesis, 4-amino-3-hydroxybutanoic acid was used instead of (4*R*,6*R*)-[6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester as in Example **1**. LC-MS: a single peak was observed at 254 nm, MH^+ calcd for the free acid $C_{20}H_{20}FN_3O_5$: 402, obtained 402. ^1H NMR (400 MHz, DMSO-d_6) δ 13.68 (s, 1H), 11.40 (s, 1H), 10.90 (s, 1H), 7.76 (dd, J = 3.2 Hz, J = 8.4 Hz,1H), 7.71 (s, 1H), 7.59 (t, J = 4.8 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, J = 4.8 Hz, J = 9.2 Hz, 1H), 4.00 (m, 1H), 3.33 (m, 2H, buried in water signals), 3.24 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H).

Example 4: 4-({5-[4,5-Difluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-3-hydroxy-butyric acid



The title compound was prepared following the procedure described in the preparation of Example **1**. In this synthesis, 4-amino-3-hydroxylbutanoic acid was used instead of (4*R*,6*R*)-[6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester as in Example **1**. LC-MS: a single peak was observed at 254 nm, MH^+ calcd for the free acid $C_{20}H_{19}F_2N_3O_5$: 420, obtained 420. ^1H NMR (400 MHz, DMSO-d_6) δ 13.55 (s, 1H), 12.10 (s, 1H), 11.15 (s, 1H), 7.67 (t, *J* = 6.0 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.14 (m, 1H), 6.68 (dd, *J* = 3.2 Hz, *J* = 8.4 Hz, 1H), 5.05 (b, 1H), 4.03 (m, 1H), 3.31 (m, 2H), 3.25 (m, 2H), 2.44 (s, 3H), 2.32 (s, 3H).

Example 5: (3*R*,5*S*)-6-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-3,5-dihydroxy-hexanoic acid, sodium salt.



Preparation of ((4*R*,6*S*)-6-Aminomethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester: Triflic anhydride 1.4mL (2.36g, 8.345mmol) was dropwise added at -78 °C to a solution of 2,6-lutidine 1.35mL (11.63mmol) and *t*-Butyl(3*R*,5*S*)-6-hydroxy-3,5-O-isopropylidene-3,5-dihydroxyhexanoate 1.981g (7.609 mmol, obtained from Kaneka Corp.) in dichloromethane (anh., 50mL) over 3 minutes. The mixture was stirred at -78 °C for 10 min, then placed on ice-slush bath and stirred at 0 °C for 45 min. The resulting pink mixture was transferred into ice-cooled solution of ammonia in methanol (7M solution, 200mL). The mixture was placed on ambient water bath and stirred at RT for 6 hours. The reaction mix was evaporated to dryness, the residue partitioned between ether (200mL) and aqueous potassium carbonate (6g in 200 mL of water), the aqueous phase re-extracted with ether (150mL).

Combined organic extracts were dried (magnesium sulfate) and evaporated. The crude product was purified on a column of silica (125g) eluting with a mix of chloroform-methanol-conc. aq. ammonia 100:10:1 (v/v) (1.5L) to give Y = 1.777g of a colorless liquid (90%), ((4*R*,6*S*)-6-Aminomethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester.

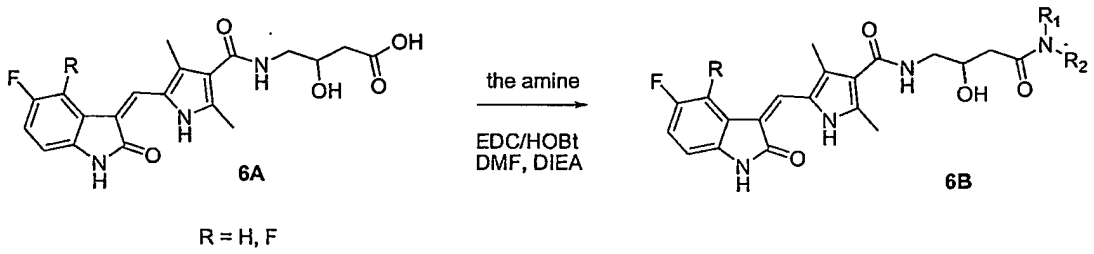
^{1}H (^{d}DMSO, 400MHz): 4.167(m, 1H), 3.741 (m, 1H), 2.484 (m, 2H), 2.384 (ddAB, J=15.2Hz, 5.1Hz, 1H), 2.201(ddAB, J=15Hz, 7.8Hz, 1H), 1.533 (br d, J=12.5Hz, 1H), 1.373 (s, 9H), 1.363 (s, 3H), 1.250 (br s, 2H), 1.223 (s, 3H)

Preparation of (3*R*,5*S*)-6-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-3,5-dihydroxy-hexanoic acid, sodium salt:

5-[(Z)-(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole -3-carboxylic acid 1-oxy-7-azabenztriazole ester 419mg (1.00mmol, prepared according to US Patent 6,653,308) was suspended in anh. dimethylacetamide (4mL) and a solution of ((4*R*,6*S*)-6-Aminomethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester 310mg (1.2 mmol) and diisopropylethyl amine 175uL (1.0mmol) in anh. DMAc (7mL) was added to the slurry. The mixture was stirred for 20 min at RT. The obtained homogenous mixture was evaporated on highvac (0.5Torr, 45 °C), the residue was taken up with methanol 10mL, sonicated for 2 minutes, then allowed to crystallize at 5 °C for 3 hours. The precipitated intermediate (acetonide-tBu ester) was collected by filtration, washed with ice-cold methanol and dried on highvac. This intermediate (485mg of an orange-yellow cryst. solid, 89.5%th.) was dissolved in neat TFA 20mL and the obtained solution was kept at RT for 15 min, then evaporated. The residue was dried on highvac for 1 day. The residue was dissolved in a mixture of methanol 100mL and THF 100mL (with 15 min stirring). 40 mL of 1M NaOH was added and the mixture was kept at RT for 30 min. The mixture was acidified with 2M HCl to pH=3. The mixture was concentrated to a small volume on rotavap to remove organic solvents, the precipitate was collected by filtration, washed with water and dried by suction, then on highvac. This precipitate (consisting of the free acid with approx 5 % of the corresponding lactone) was dissolved in a mixture of

methanol (200mL), water (30mL) and 1M NaOH (0.96mL) with stirring and gentle heating to reflux for 3 minutes. The mixture was stirred at RT for additional 15 minutes, then saturated with CO2 (g), evaporated to dryness and dried on highvac to give Y=376.5mg (90%) of an orange solid, (3*R*,5*S*)-6-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-3,5-dihydroxy-hexanoic acid, sodium salt.
LC/MS(+ESI): 446 (M+1)
^{1}H (D2O, 400MHz): 6.655(br d, J=9.4Hz, 1H), 6.594 (m, 2H), 6.292(dd, J=8.2Hz, 4.7Hz, 1H), 4.155 (m, 1H), 3.891 (m, 1H), 3.405(dd, J=14.1Hz, 3.9Hz, 1H), 3.195 (dd, J=15.7Hz, 7.5Hz, 1H), 2.429 (ddAB, J=14.9Hz, 5.0Hz, 1H), 2.329 (ddAB, J=14.9Hz, 8.2Hz, 1H), 1.782 (m, 2H)

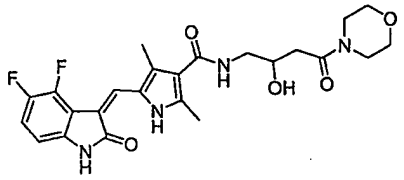
Examples 6-8: The general procedure for the synthesis of amides of Examples **3** and **4** is shown in Scheme 2 below:



Scheme 2

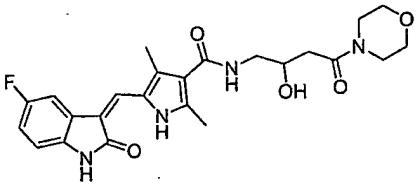
A corresponding amine (0.3 mmol) was added to a solution of compound **6A** (80 mg, 0.2 mmol), EDC (0.25 mmol), HOBt (0.25 mmol), and DIEA (1 mmol) in DMF (3 mL). After the solution was stirred at 25 °C overnight, DMF was removed via evaporation under reduced pressure. The resulting residue was suspended in ethyl acetate (200 mL), washed by saturated $NaHCO_3$ (3x) and brine (3x), and dried over Na_2SO4. The ethyl acetate was removed under vacuum to give the crude product. This crude material was subjected to preparative HPLC to give the final product **6B**, which was subsequently characterized by LC-MS and NMR spectroscopy.

Example 6: 5-[4,5-Difluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-4-morpholin-4-yl-4-oxo-butyl)-amide.



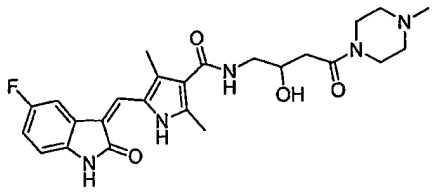
Preparative HPLC gave 70 mg of the title compound (75%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{26}F_2N_4O_5$: 489, obtained: 489. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.55 (s, 1H), 11.20 (s, 1H), 7.64 (t, J = 6.0 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.13 (m, 1H), 6.70 (dd, J = 3.2 Hz, J = 8.4 Hz, 1H), 4.99 (s, 1H), 4.04 (m, 1H), 3.20-3.60 (m, 12H), 2.45 (s, 3H), 2.32 (s, 3H).

Example 7: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-4-morpholin-4-yl-4-oxo-butyl)-amide



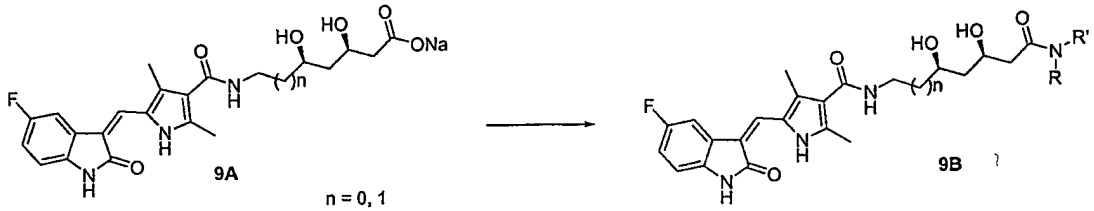
Preparative HPLC gave 50 mg of the title compound (53%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{27}FN_4O_5$: 471, obtained: 471. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.69 (s, 1H), 10.91 (s, 1H), 7.76 (dd, J = 3.2 Hz, J = 9.2 Hz, 1H), 7.71 (s, 1H), 7.57 (t, J = 6.0 Hz, 1H), 6.95 (m, 1H), 6.83 (dd, J = 4.8 Hz, J = 8.8 Hz, 1H), 4.98 (d, J = 5.2 Hz, 1H), 4.04 (m, 1H), 3.53 (m, 5H), 3.45 (m, 4H), 3.28 (m, 3H), 2.43 (s, 3H), 2.41 (s, 3H).

Example 8: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-hydroxy-4-(4-methyl-piperazin-1-yl)-4-oxo-butyl]-amide



Preparative HPLC gave 55 mg of the title compound (57%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{25}H_{30}FN_5O_4$: 484, obtained: 484. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.65 (s, 1H), 10.90 (s, 1H), 7.74 (m, 2H), 7.71 (m, 1H), 7.54 (m, 1H), 6.92 (m, 1H), 6.83 (m, 1H), 4.95 (s, 1H), 4.04 (m, 1H), 3.44 (m, 4H), 3.25 (m, 4H, buried in water signals), 2.43 (s, 3H), 2.41 (s, 3H), 2.25 (m, 4H), 2.16 (s, 3H).

Examples 9-16: The general procedure for the synthesis of amides of Examples **1** and **5** is shown in Scheme 3 below:



Method 1: i, HOBt (5 equiv), EDC (3 equiv), DMF; ii, the amine (5 equiv)
Method 2: i, TBDMS-Cl (5 equiv), DMAP (5 equiv), DMF; ii, EDC (3 equiv), HOBt (3 equiv), the amine (2 equiv); iii, TBAF, THF

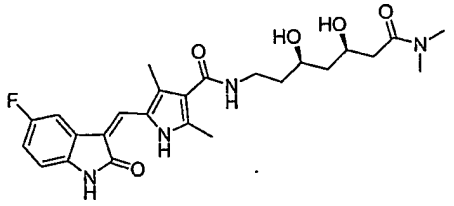
Scheme 3

Method 1: EDC (1 mmol), and HOBt (0.6 mmol) were added to a solution of compound **9A** (0.2 mmol) in DMF (3 mL). After the solution was stirred at 25 °C for 3 h, the corresponding amine (1.0 mmol) was added, and the solution was stirred at 25 °C overnight. If the reaction was not complete, the solution was stirred at 50 °C for another couple of hours. This DMF solution was directly subjected to preparative HPLC to obtain the final product **9B**, which was subsequently characterized by LC-MS and proton NMR spectroscopy.

Method 2: TBDMS-Cl (1.0 mmol), and DMAP (1.0 mmol) were added to a solution of compound **9A** (0.2 mmol) in DMF (3 mL). After the solution was stirred at 25 °C for 5 h (LC-MS demonstrated that a mixture of mono- and

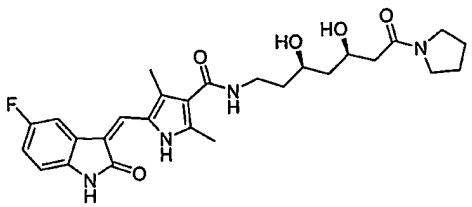
disilyl ether products was formed), EDC (1 mmol), HOBt (0.6 mmol), and the corresponding amine (0.4 mmol) were added to the solution. The solution was continuously stirred at 25 °C overnight (LC-MS demonstrated that a mixture of the amides of the corresponding mono- and di-silyl ether products was formed). After the solvent was removed via evaporation under reduced pressure, the resulting residue was suspended in ethyl acetate (100 mL), washed with saturated $NaHCO_3$ (3x), and brine (3x). The organic solvent was then evaporated under vacuum to give the crude silyl ether amide products. TBAF (3 equiv, 1M in THF) was added to a solution of this crude material in THF. After stirring at 25 °C for 30 min., the THF was removed under reduced pressure. The residue was suspended in ethyl acetate (100 mL), washed with brine (3x). The organic solvent was then evaporated under reduced pressure, and the resulting residue was directly subjected to preparative HPLC to obtain the final product **9B**, which was subsequently characterized by LC-MS and proton NMR spectroscopy.

Example 9: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((3*R*,5*R*)-6-dimethylcarbamoyl-3,5-dihydroxy-hexyl)-amide



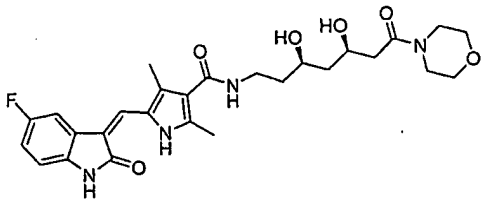
This compound was prepared via **Method 2**. An amount of 65 mg (64%) product was obtained after preparative HPLC. LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{25}H_{31}FN_4O_5$: 487, obtained: 487. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.67 (s, 1H), 10.90 (s, 1H), 7.76 (dd, *J* = 2.8 Hz, *J* = 9.2 Hz, 1H), 7.71 (s, 1H), 7.63 (t, *J* = 5.6 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.8 Hz, 1H), 4.72 (d, *J* = 4.4 Hz, 1H), 4.67 (d, *J* = 4.8 Hz, 1H), 4.00 (m, 1H), 3.71 (m, 1H), 3.31 (m, 2H), 2.96 (s, 3H), 2.80 (s, 1H), 2.42 (s, 3H), 2.40 (s, 3H), 2.39 (m, 2H), 1.65(m, 1H), 1.52 (m, 3H).

Example 10: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((3*R*,5*R*)-3,5-dihydroxy-7-oxo-7-pyrrolidin-1-yl-heptyl)-amide



This compound was prepared via **Method 1**. An amount of 55 mg (61%) product was obtained after preparative HPLC. LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{27}H_{33}FN_4O_5$: 513, obtained: 513. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.66 (s, 1H), 10.90 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.2 Hz, 1H), 7.71 (s, 1H), 7.63 (t, *J* = 5.6 Hz, 1H), 6.91 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.8 Hz, 1H), 4.75 (d, *J* = 4.4 Hz, 1H), 4.68 (d, *J* = 4.8 Hz, 1H), 4.03 (m, 1H), 3.70 (m, 1H), 3.40 (m, 2H), 3.26 (m, 4H), 2.42 (s, 3H), 2.40 (s, 3H), 2.34 (m, 2H), 1.83 (m, 2H), 1.74 (m, 2H), 1.65 (m, 1H), 1.52 (m, 3H).

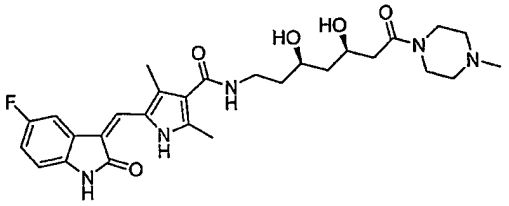
Example 11: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((3*R*,5*R*)-3,5-dihydroxy-7-morpholin-4-yl-7-oxo-heptyl)-amide



This compound was prepared via **Method 2**. An amount of 72 mg (66%) product was obtained after preparative HPLC. LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{27}H_{33}FN_4O_6$: 529, obtained: 529. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.66 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.2 Hz, 1H), 7.71 (s, 1H), 7.63 (t, *J* = 5.6 Hz, 1H), 6.91 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.8 Hz, 1H), 6.70 (b, 1H), 4.71 (d, *J* = 4.4 Hz, 1H), 4.67 (d, *J* = 4.8 Hz, 1H), 4.01 (m, 1H), 3.70

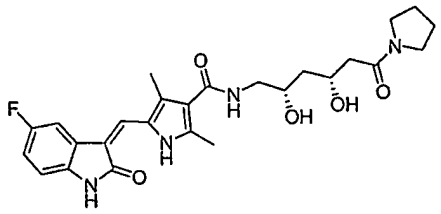
(m, 1H), 3.51 (m, 5H), 3.45 (m, 3H), 3.42-3.24 (m, 4H), 2.42 (s, 3H), 2.40 (s, 3H), 1.65 (m, 1H), 1.52 (m, 3H).

Example 12: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(3*R*,5*R*)-3,5-dihydroxy-7-(4-methyl-piperazin-1-yl)-7-oxo-heptyl]-amide



This compound was prepared via **Method 2**. An amount of 30 mg (27%) product was obtained after preparative HPLC. LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{28}H_{36}FN_5O_5$: 542, obtained: 542. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.66 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.2 Hz, 1H), 7.70 (s, 1H), 7.63 (t, *J* = 5.6 Hz, 1H), 6.91 (m, 1H), 6.84 (dd, *J* = 4.8 Hz, *J* = 8.8 Hz, 1H), 4.70 (b, 2H), 4.01 (m, 1H), 3.70 (m, 1H), 3.43 (m, 4H), 3.30 (m, 4H), 2.42 (s, 3H), 2.40 (s, 3H), 2.26 (m, 2H), 2.21 (m, 2H), 2.15 (s, 3H), 1.65 (m, 1H), 1.52 (m, 3H).

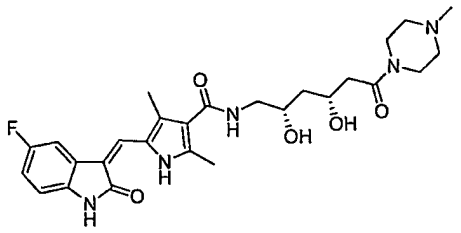
Example 13: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((2*S*,4*R*)-2,4-dihydroxy-6-oxo-6-pyrrolidin-1-yl-hexyl)-amide



This compound was prepared via **Method 1**. An amount of 66 mg (54%) product was obtained after preparative HPLC. LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{29}FN_4O_5$: 473, obtained: 473. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.72 (s, 1H), 10.90 (s, 1H), 7.77 (dd, *J* = 2.4 Hz, *J* = 9.2 Hz, 1H),

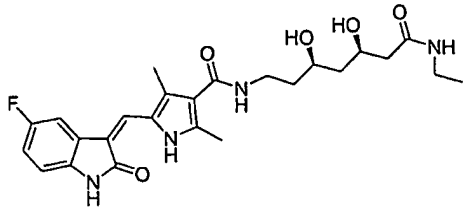
7.72 (s, 1H), 7.49 (t, J = 5.6 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, J = 4.4 Hz, J = 8.4 Hz, 1H), 4.80 (s, 1H), 4.78 (s, 1H), 4.05 (m, 1H), 3.76 (m, 1H), 3.41 (m, 2H), 3.26 (m, 4H), 2.44 (s, 3H), 2.42 (s, 3H), 2.36 (m, 2H), 1.85 (m, 2H), 1.75 (m, 2H), 1.61 (m, 1H), 1.50 (m, 1H).

Example 14: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(2S,4R)-2,4-dihydroxy-6-(4-methyl-piperazin-1-yl)-6-oxo-hexyl]-amide



This compound was prepared via **Method 2**. An amount of 97 mg (75%) product was obtained after preparative HPLC. LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{27}H_{34}FN_5O_5$: 528, obtained: 528. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.72 (s, 1H), 10.90 (s, 1H), 7.75 (dd, J = 2.4 Hz, J = 9.6 Hz, 1H), 7.70 (s, 1H), 7.48 (t, J = 5.6 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, J = 4.4 Hz, J = 8.4 Hz, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 4.05 (m, 1H), 3.77 (m, 1H), 3.43 (m, 4H), 3.25 (m, 2H), 3.15 (m, 4H), 2.44 (s, 3H), 2.41 (s, 3H), 2.27 (m, 2H), 2.20 (m, 2H), 2.15 (s, 3H).

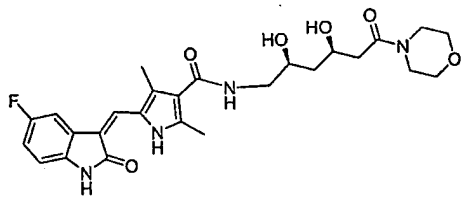
Example 15: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((3*R*,5*R*)-6-ethylcarbamoyl-3,5-dihydroxy-hexyl)-amide



This compound was prepared via **Method 2**. An amount of 40 mg (40%) product was obtained after preparative HPLC. LC-MS: single peak at 254 nm,

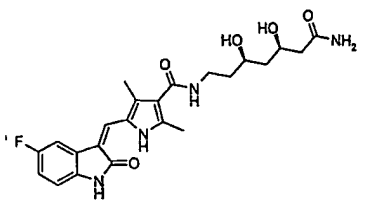
MH^+ calcd for $C_{25}H_{31}FN_4O_5$: 487, obtained: 487. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.90 (s, 1H), 7.78 (t, *J* = 5.6 Hz, 1H), 7.75 (dd, *J* = 2.8 Hz, *J* = 9.2 Hz, 1H), 7.70 (s, 1H), 7.61 (t, *J* = 5.6 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.8 Hz, 1H), 4.76 (s, 1H), 4.67 (s, 1H), 3.96 (m, 1H), 3.69 (m, 1H), 3.28 (m, 2H), 3.04 (m, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 2.16 (m, 2H), 1.65 (m, 1H), 1.52 (m, 3H), 0.99 (t, 7.6 Hz, 3H).

Example 16: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((2*S*,4*R*)-2,4-dihydroxy-6-morpholin-4-yl-7-oxo-heptyl)-amide

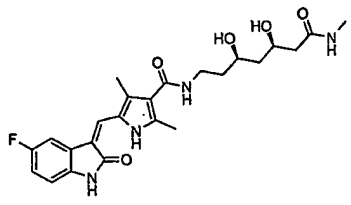


This compound was prepared via **Method 2**. An amount of 87 mg (69%) product was obtained after preparative HPLC. LC-MS: single peak at 254 nm, MH^+ calcd for $C_{26}H_{31}FN_4O_6$: 515, obtained: 515. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.69 (s, 1H), 10.88 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.2 Hz, 1H), 7.71 (s, 1H), 7.48 (t, *J* = 4.0 Hz, 1H), 6.91 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 9.2 Hz, 1H), 4.84 (d, *J* = 4.4 Hz, 1H), 4.74 (d, *J* = 4.4 Hz, 1H), 4.05 (m, 1H), 3.77 (m, 1H), 3.50 (m, 9H), 3.25 (m, 3H), 2.44 (s, 3H), 2.41 (s, 3H), 1.58 (m, 2H).

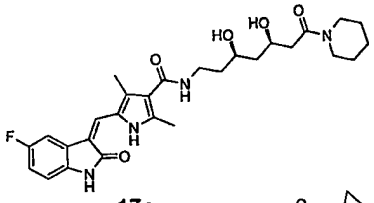
Example 17. Further amide examples of Example 1. The following examples **17a-f** can be made by those skilled in the art following the above procedure and/or known procedures.



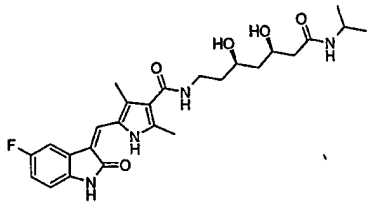
17a



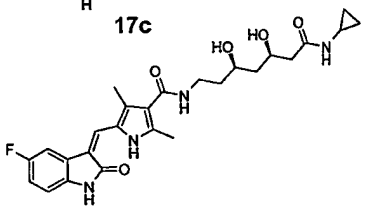
17b



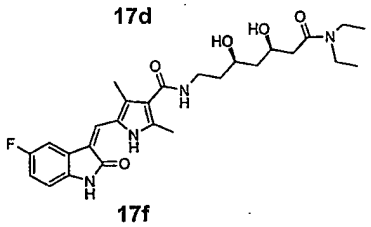
17c



17d

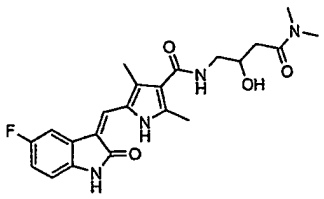


17e

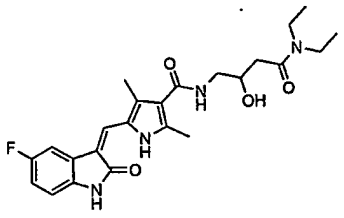


17f

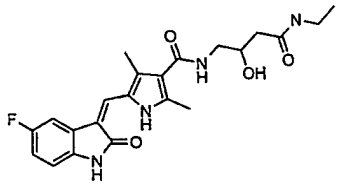
Example 18. Further amide examples of Example 3. The following examples **18a-f** can be made by those skilled in the art following the above procedure and/or known procedures.



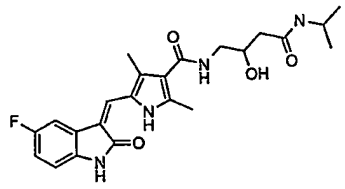
18a



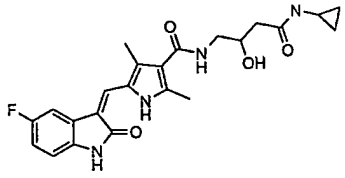
18b



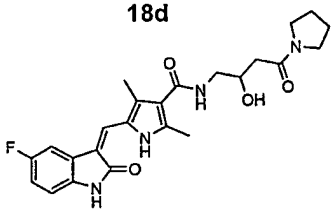
18c



18d

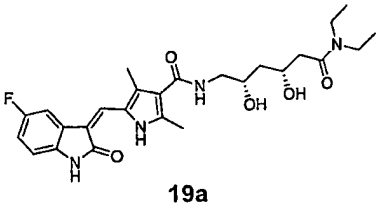


18e

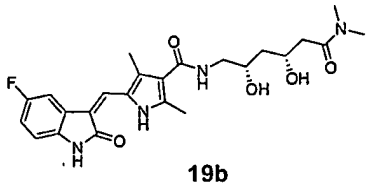


18f

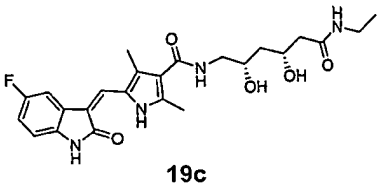
Example 19. Further amide examples of Example 5. The following examples **19a-d** can be made by those skilled in the art following the above procedure and/or known procedures.



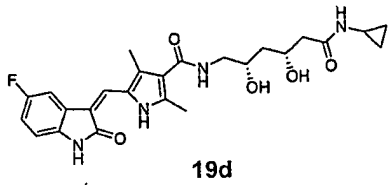
19a



19b



19c

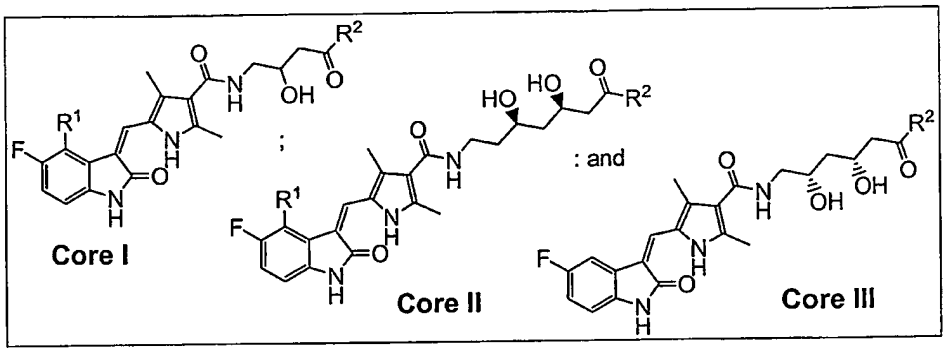


19d

The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on

the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

Example 20-269. Still further amide examples of Examples 1-5 are shown in the following table.



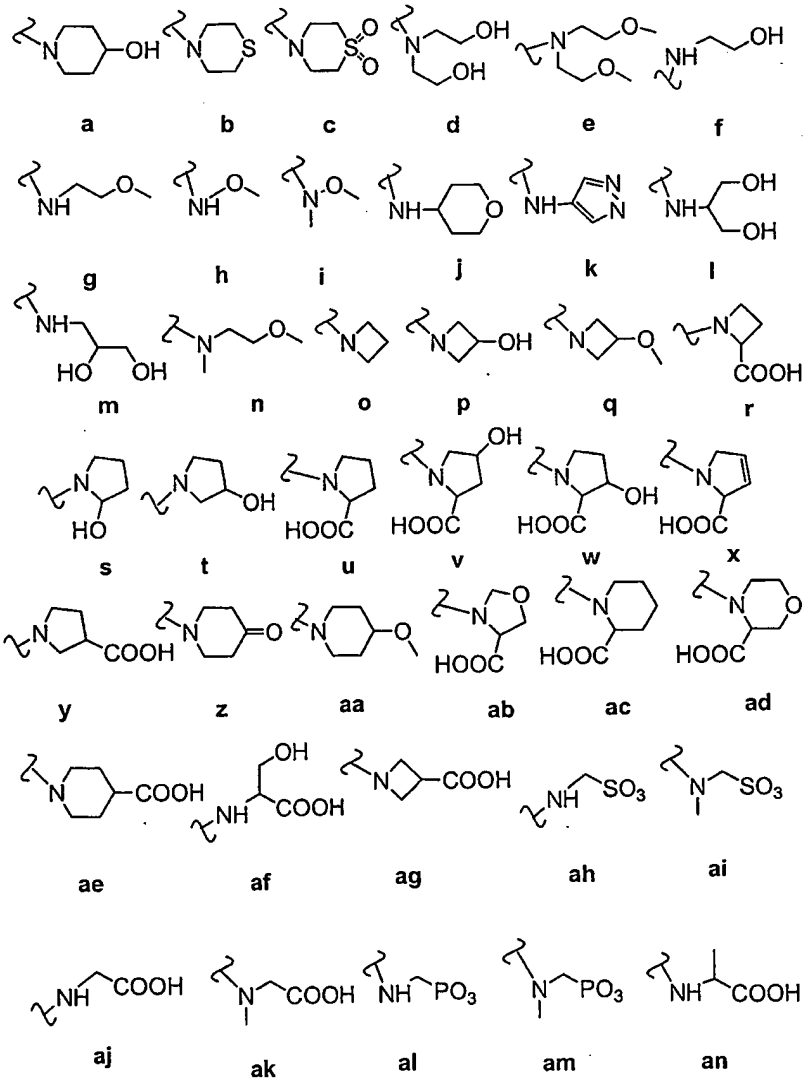
Ex#	core	R1	R2	Ex#	core	R1	R2	Ex#	core	R1	R2
20	I	H	a	70	I	F	a	120	III	H	a
21	I	H	b	71	I	F	b	121	III	H	b
22	I	H	c	72	I	F	c	122	III	H	c
23	I	H	d	73	I	F	d	123	III	H	d
24	I	H	e	74	I	F	e	124	III	H	e
25	I	H	f	75	I	F	f	125	III	H	f
26	I	H	g	76	I	F	g	126	III	H	g
27	I	H	h	77	I	F	h	127	III	H	h
28	I	H	i	78	I	F	i	128	III	H	i
29	I	H	j	79	I	F	j	129	III	H	j
30	I	H	k	80	I	F	k	130	III	H	k
31	I	H	l	81	I	F	l	131	III	H	l
32	I	H	m	82	I	F	m	132	III	H	m
33	I	H	n	83	I	F	n	133	III	H	n
34	I	H	o	84	I	F	o	134	III	H	o
35	I	H	p	85	I	F	p	135	III	H	p
36	I	H	q	86	I	F	q	136	III	H	q

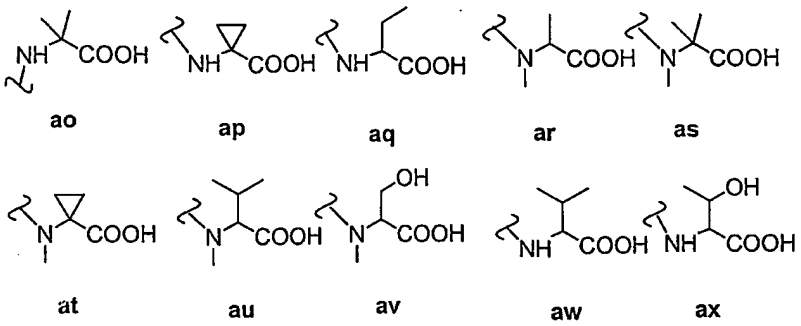
Ex#	core	R1	R2	Ex#	core	R1	R2	Ex#	core	R1	R2
37	I	H	r	87	I	F	r	137	III	H	r
38	I	H	s	88	I	F	s	138	III	H	s
39	I	H	t	89	I	F	t	139	III	H	t
40	I	H	u	90	I	F	u	140	III	H	u
41	I	H	v	91	I	F	v	141	III	H	v
42	I	H	w	92	I	F	w	142	III	H	w
43	I	H	x	93	I	F	x	143	III	H	x
44	I	H	y	94	I	F	y	144	III	H	y
45	I	H	z	95	I	F	z	145	III	H	z
46	I	H	aa	96	I	F	aa	146	III	H	aa
47	I	H	ab	97	I	F	ab	147	III	H	ab
48	I	H	ac	98	I	F	ac	148	III	H	ac
49	I	H	ad	99	I	F	ad	149	III	H	ad
50	I	H	ae	100	I	F	ae	150	III	H	ae
51	I	H	af	101	I	F	af	151	III	H	af
52	I	H	ag	102	I	F	ag	152	III	H	ag
53	I	H	ah	103	I	F	ah	153	III	H	ah
54	I	H	ai	104	I	F	ai	154	III	H	ai
55	I	H	aj	105	I	F	aj	155	III	H	aj
56	I	H	ak	106	I	F	ak	156	III	H	ak
57	I	H	al	107	I	F	al	157	III	H	al
58	I	H	am	108	I	F	am	158	III	H	am
59	I	H	an	109	I	F	an	159	III	H	an
60	I	H	ao	110	I	F	ao	160	III	H	ao
61	I	H	ap	111	I	F	ap	161	III	H	ap
62	I	H	aq	112	I	F	aq	162	III	H	aq
63	I	H	ar	113	I	F	ar	163	III	H	ar
64	I	H	as	114	I	F	as	164	III	H	as
65	I	H	at	115	I	F	at	165	III	H	at
66	I	H	au	116	I	F	au	166	III	H	au
67	I	H	av	117	I	F	av	167	III	H	av
68	I	H	aw	118	I	F	aw	168	III	H	aw
69	I	H	ax	119	I	F	ax	169	III	H	ax

Ex#	core	R1	R2	Ex#	core	R1	R2
170	II	H	a	220	II	F	a
171	II	H	b	221	II	F	b
172	II	H	c	222	II	F	c
173	II	H	d	223	II	F	d
174	II	H	e	224	II	F	e
175	II	H	f	225	II	F	f
176	II	H	g	226	II	F	g
177	II	H	h	227	II	F	h
178	II	H	i	228	II	F	i
179	II	H	j	229	II	F	j
180	II	H	k	230	II	F	k
181	II	H	l	231	II	F	l
182	II	H	m	232	II	F	m
183	II	H	n	233	II	F	n
184	II	H	o	234	II	F	o
185	II	H	p	235	II	F	p
186	II	H	q	236	II	F	q
187	II	H	r	237	II	F	r
188	II	H	s	238	II	F	s
189	II	H	t	239	II	F	t
190	II	H	u	240	II	F	u
191	II	H	v	241	II	F	v
192	II	H	w	242	II	F	w
193	II	H	x	243	II	F	x
194	II	H	y	244	II	F	y
195	II	H	z	245	II	F	z
196	II	H	aa	246	II	F	aa
197	II	H	ab	247	II	F	ab
198	II	H	ac	248	II	F	ac
199	II	H	ad	249	II	F	ad
200	II	H	ae	250	II	F	ae
201	II	H	af	251	II	F	af
202	II	H	ag	252	II	F	ag
203	II	H	ah	253	II	F	ah
204	II	H	ai	254	II	F	ai
205	II	H	aj	255	II	F	aj
206	II	H	ak	256	II	F	ak
207	II	H	al	257	II	F	al
208	II	H	am	258	II	F	am
209	II	H	an	259	II	F	an
210	II	H	ao	260	II	F	ao
211	II	H	ap	261	II	F	ap
212	II	H	aq	262	II	F	aq

Ex#	core	R1	R2	Ex#	core	R1	R2
213	II	H	ar	263	II	F	ar
214	II	H	as	264	II	F	as
215	II	H	at	265	II	F	at
216	II	H	au	266	II	F	au
217	II	H	av	267	II	F	av
218	II	H	aw	268	II	F	aw
219	II	H	ax	269	II	F	ax

In the above table, R^2 is selected from the following radicals:





ao ap aq ar as

at au av aw ax

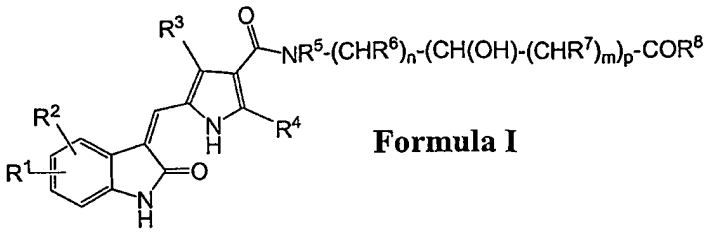
These amide examples **20-269** can be made by those skilled in the art following the above procedure and/or known procedures.

Cellular Assay: HUVEC: VEGF induced proliferation

The compounds were assayed for cellular activity in the VEGF induced proliferation of HUVEC cells. HUVEC cells (Cambrex, CC-2517) were maintained in EGM (Cambrex, CC-3124) at 37°C and 5% CO_2. HUVEC cells were plated at a density 5000 cells/well (96 well plate) in EGM. Following cell attachment (1hour) the EGM-medium was replaced by EBM (Cambrex, CC-3129) + 0.1% FBS (ATTC , 30-2020) and the cells were incubated for 20 hours at 37°C. The medium was replaced by EBM +1% FBS, the compounds were serial diluted in DMSO and added to the cells to a final concentration of 0 – 5,000 nM and 1% DMSO. Following a 1 hour pre-incubation at 37°C cells were stimulated with 10ng/ml VEGF (Sigma, V7259) and incubated for 45 hours at 37°C. Cell proliferation was measured by BrdU DNA incorporation for 4 hours and BrdU label was quantitated by ELISA (Roche kit, 16472229) using 1M H_2SO_4 to stop the reaction. Absorbance was measured at 450nm using a reference wavelength at 690nm.

What is claimed is:

1. A compound represented by Formula (I):



Formula I

wherein:

R^1 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, amino, (C1-C6) alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted (C6-C10) aryl;

R^2 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, (C2-C8) alkoxyalkyl, amino, (C1-C6) alkylamino, (C6-C10) arylamino;

R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C6-C10) aryl, (C5-C10) heteroaryl, and amide;

R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen and (C1-C6) alkyl;

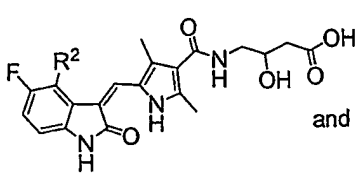
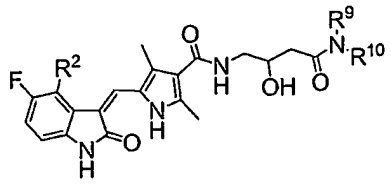
each R^7 is independently selected from the group consisting of hydrogen, (C1-C6) alkyl and hydroxyl;

R^8 is selected from the group consisting of hydroxy, (C1-C6) O-alkyl, (C3-C8) O-cycloalkyl, and NR^9R^{10}; where R^9 and R^{10} are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^9 and R^{10} together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; and

n and **m** are independently 0, 1, 2, or 3; p is 1, 2, or 3;

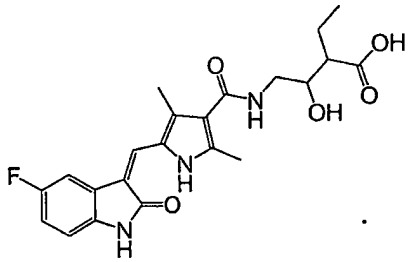
or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug thereof.

2. The compound, salt, tautomer, or prodrug according to claim 1 selected from the group represented by the following structures:

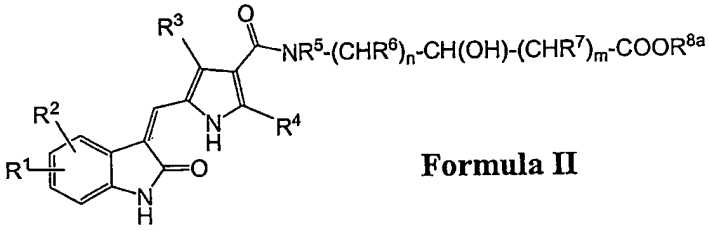

and


wherein R^2 is selected from the group consisting of hydrogen and fluoro.

3. The compound, salt, tautomer, or prodrug according to claim 1 represented by the following structure:



4. The compound, salt, tautomer, or prodrug according to claim 1 represented by Formula (II):



Formula II

wherein R^{8a} is selected from the group consisting of hydrogen, (C1-C6) alkyl, and (C3-C8) cycloalkyl.

5. The compound, salt, tautomer, or prodrug according to claim 4, wherein:

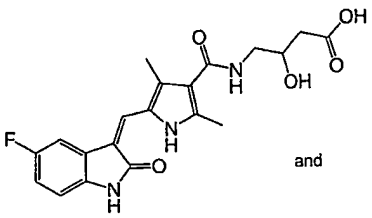
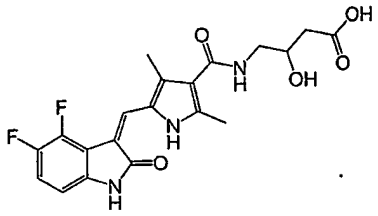
R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro;

R^3 and R^4 are methyl;

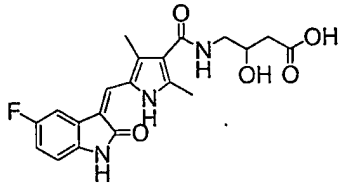
R^5, R^6, R^7 and R^{8a} are hydrogen; and

n and **m** are independently 0, 1, or 2.

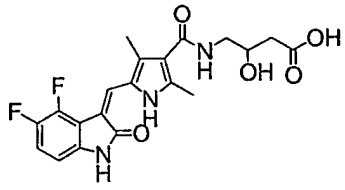
6. The compound, salt, tautomer, or prodrug according to claim 5 selected from the group consisting of:


and


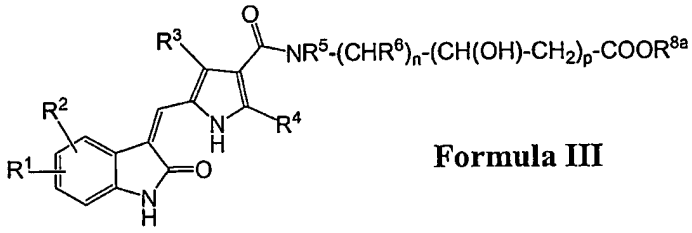
7. The compound, salt, tautomer, or prodrug according to claim 5 represented by the following structure:



8. The compound, salt, tautomer, or prodrug according to claim 5 represented by the following structure:



9. A compound, salt, tautomer, or prodrug according to claim 1 represented by Formula (III):



Formula III

wherein R^{8a} is selected from the group consisting of hydrogen, (C1-C6) alkyl, and (C3-C8) cycloalkyl.

10. The compound, salt, tautomer, or prodrug according to claim 9, wherein:

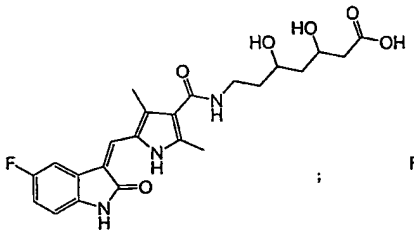
R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro;

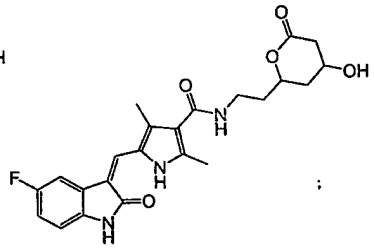
R^3 and R^4 are methyl;

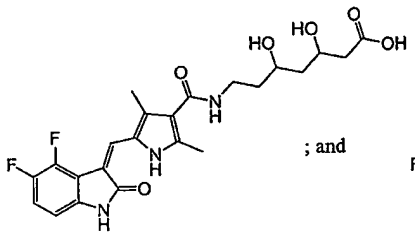
R^5, R^6, and R^{8a} are hydrogen; and

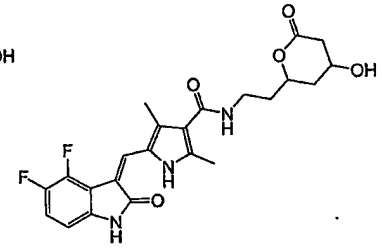
n and **p** are independently 1, or 2.

11. The compound, salt, tautomer, or prodrug according to claim 10 selected from the group consisting of:

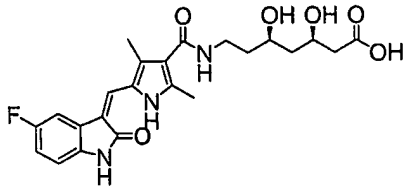

;


;

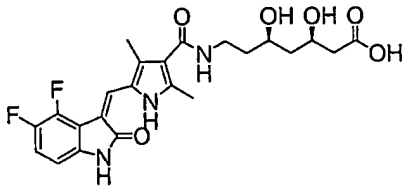

; and


.

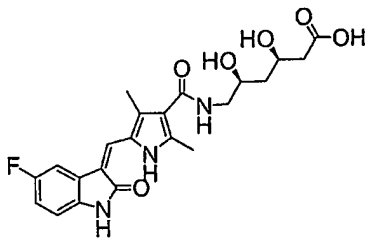
12. The compound, salt, tautomer, or prodrug according to claim 10 represented by the following structure:


.

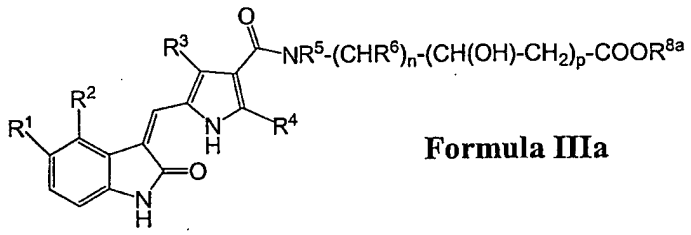
13. The compound, salt, tautomer, or prodrug according to claim 10 represented by the following structure:


.

14. The compound, salt, tautomer, or prodrug according to claim 10 represented by the following structure:



15. A compound, salt, tautomer, or prodrug according to claim 9 represented by Formula (**IIIa**):



Formula IIIa

wherein:

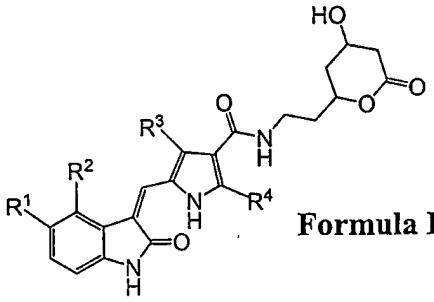
R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro;

R^3 and R^4 are methyl;

R^5, R^6, and R^{8a} are hydrogen; and

n and **p** are 2.

16. A compound, salt, tautomer, or prodrug according to claim 15 represented by Formula (**IIIb**):



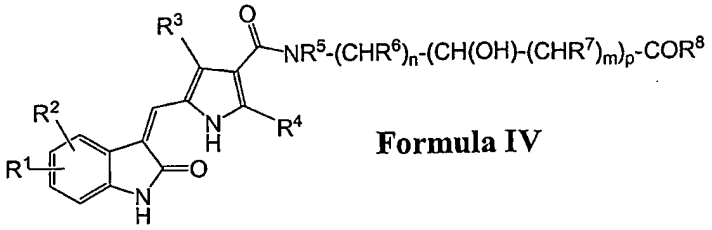
Formula IIIb

wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro; and

R^3 and R^4 are methyl.

17. A compound, salt, tautomer, or prodrug according to claim 1 represented by Formula (**IV**):



Formula IV

wherein R^8 is NR^9R^{10}.

18. The compound, salt, tautomer, or prodrug of claim 17, wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, cyano;

R^3, R^4, R^5 and R^6 are independently hydrogen or (C1-C6))alkyl;

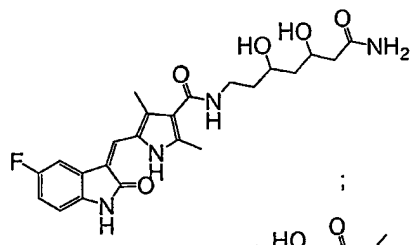
R^7 is hydrogen, or hydroxyl;

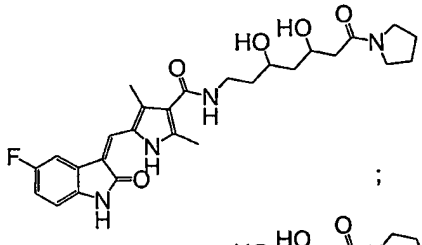
n, and **p** are independently 1, or 2;

m is 0 or 1; and

R^9 and R^{10} are selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^9 and R^{10} together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids.

19. The compound, salt, tautomer, or prodrug according to claim 18 selected from the group represented by the following structures:


;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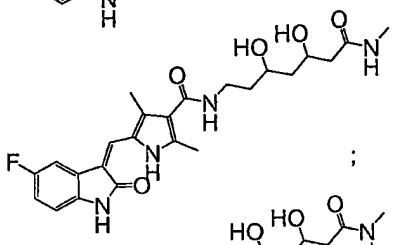
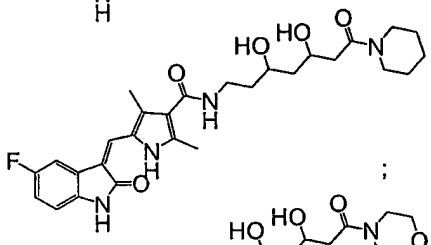

;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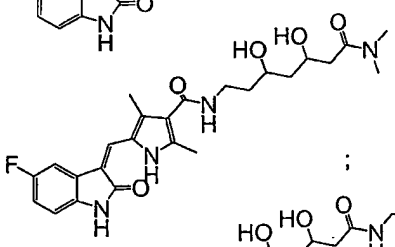
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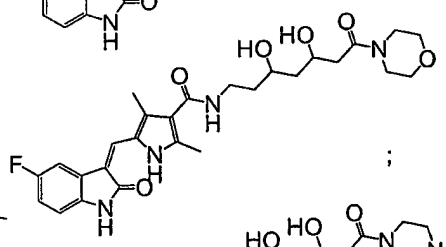
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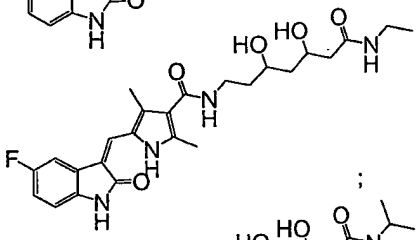
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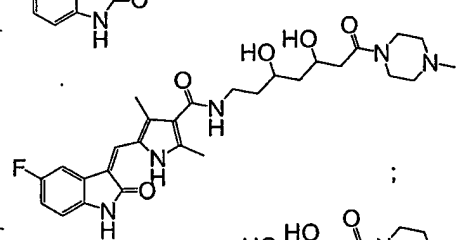
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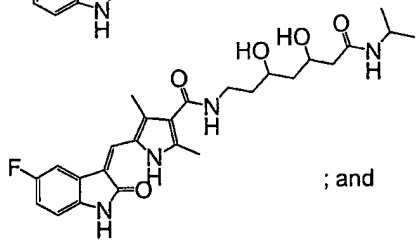
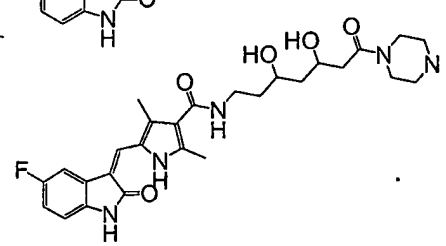

; and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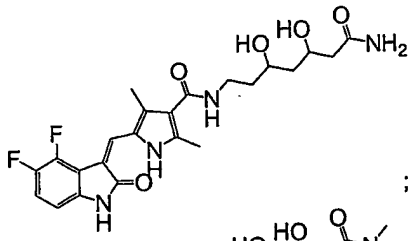
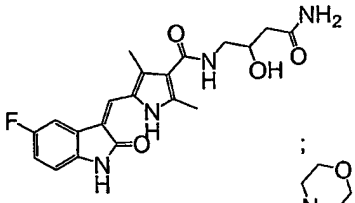
20. The compound, salt, tautomer, or prodrug according to claim 18 selected from the group represented by the following structures:


;

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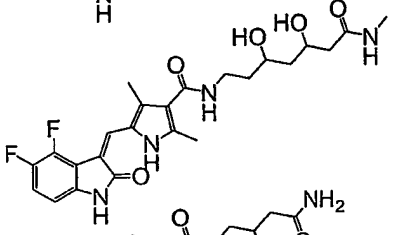
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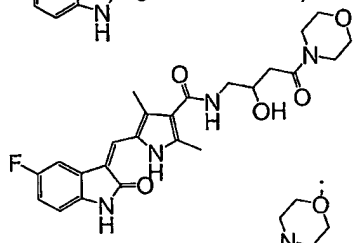
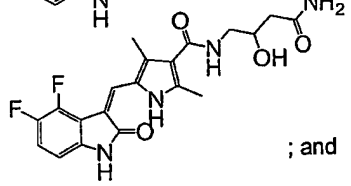
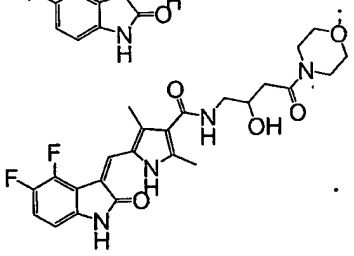

;

; and

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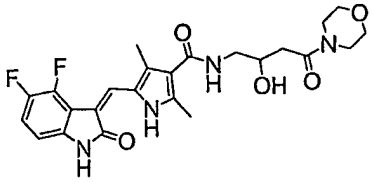
21. The compound, salt, tautomer, or prodrug according to claim 18 represented by the following structure: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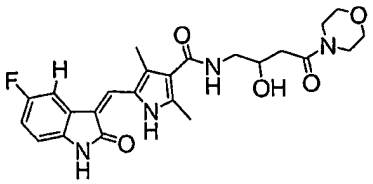
22. The compound, salt, tautomer, or prodrug according to claim 18 represented by the following structure: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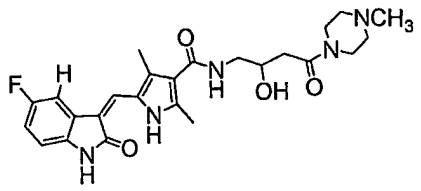
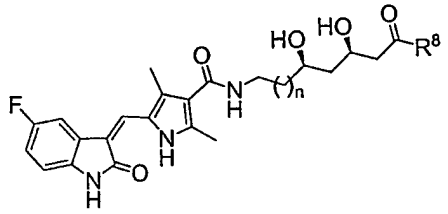
23. The compound, salt, tautomer, or prodrug according to claim 18 represented by the followingstructure:

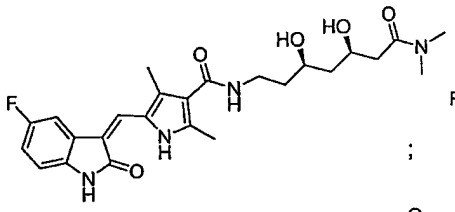


24. The compound, salt, tautomer, or prodrug according to claim 18 represented by the following structure:



wherein n is 0, 1, or 2.

25. The compound, salt, tautomer, or prodrug according to claim 24 selected from the group represented by the following structures: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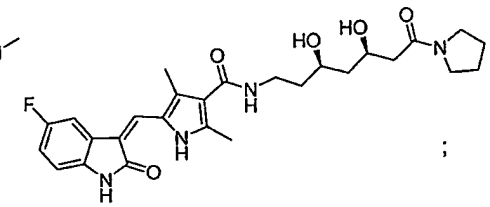
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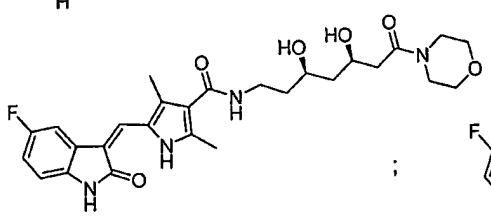
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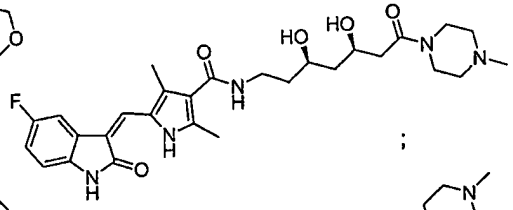
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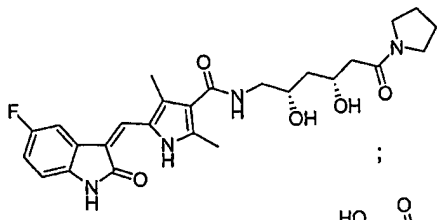
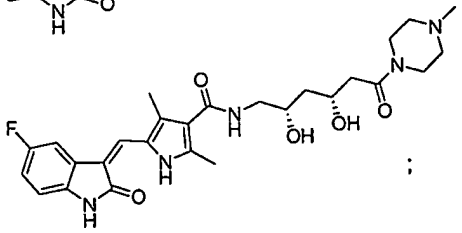
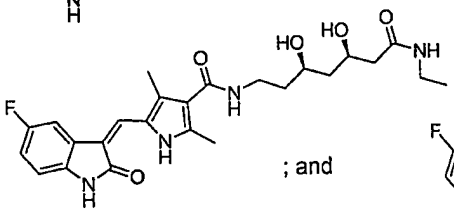
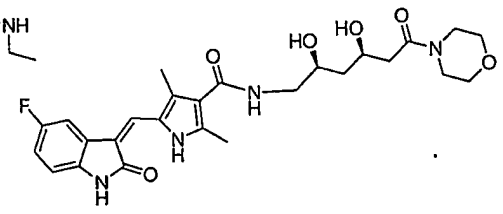

;


;


; and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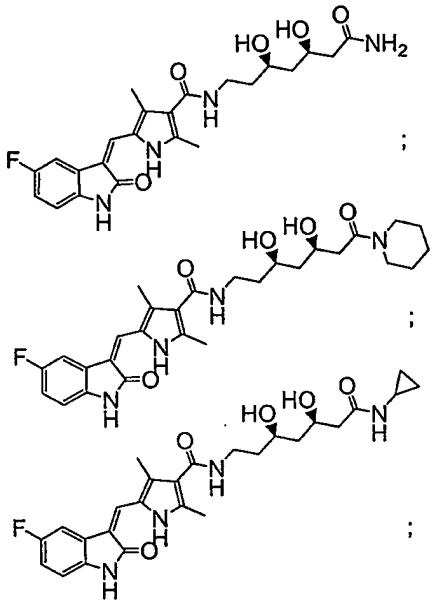
26. The compound, salt, tautomer, or prodrug according to claim 24 selected from the group represented by the following structures: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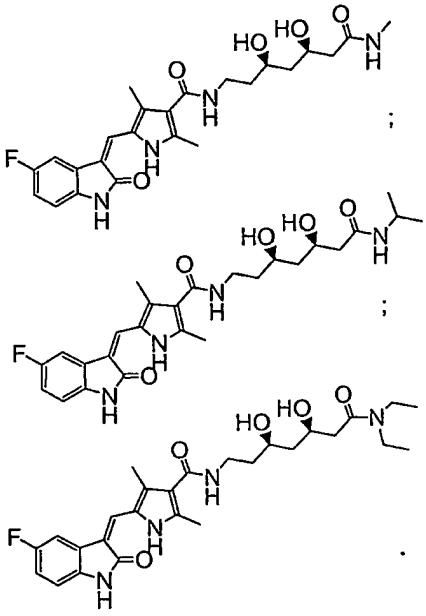
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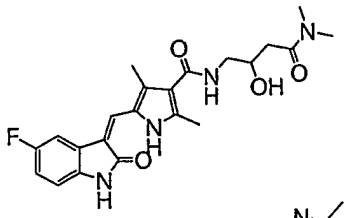
27. The compound, salt, tautomer, or prodrug according to claim 18 selected from the group represented by the following structures: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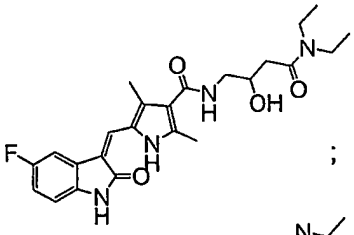
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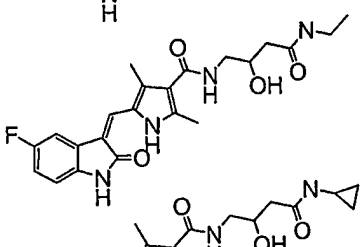
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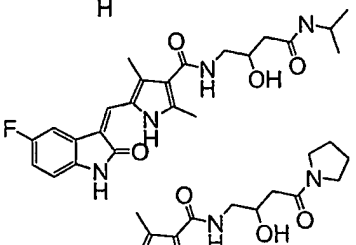
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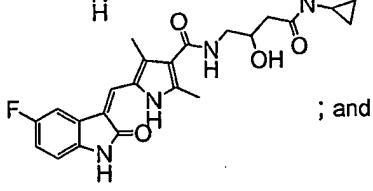
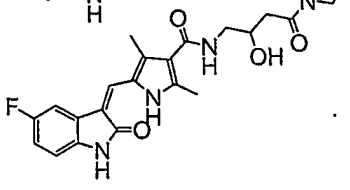
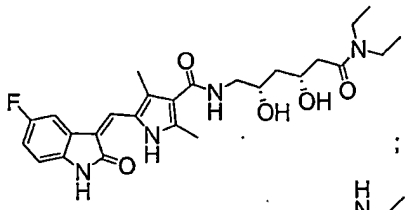
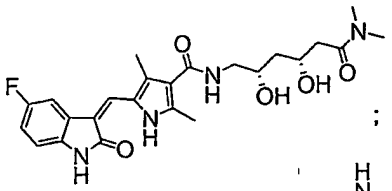
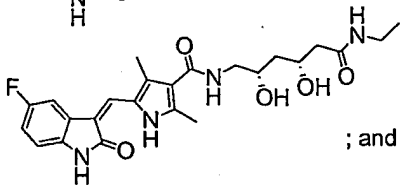

; and

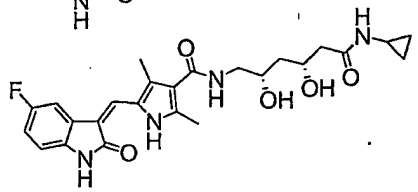

.

28. The compound, salt, tautomer, or prodrug according to claim 18 selected from the group represented by the following structures:


;


;


; and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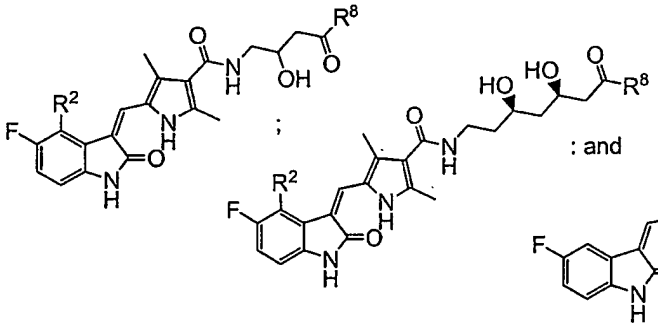
29. The compound, salt, tautomer, or prodrug according to claim 18 selected from the group represented by the following structures:

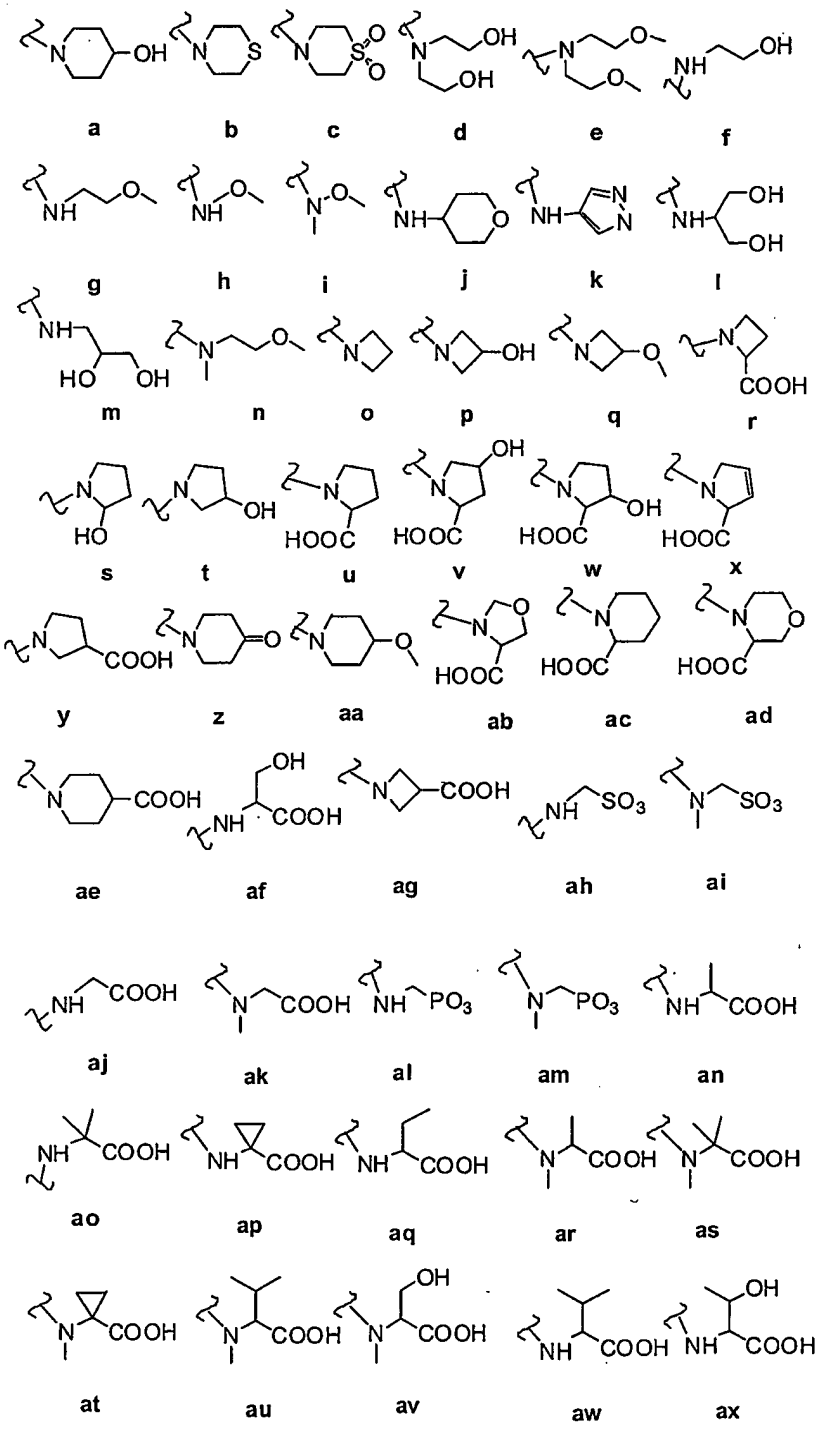

;

: and

wherein:

R^2 is selected from the group consisting of hydrogen and fluoro; and

R^8 is selected from the group consisting of radicals represented by the following structures: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30. The compound, salt, tautomer, or prodrug according to any of claims 1-29 with the following provisios:

the compound, salt, tautomer, or prodrug of claim 2 is excluded or
the compound, salt, tautomer, or prodrug of claim 3 is excluded or
the compound, salt, tautomer, or prodrug of claim 4 is excluded or
the compound, salt, tautomer, or prodrug of claim 5 is excluded or
the compound, salt, tautomer, or prodrug of claim 6 is excluded or
the compound, salt, tautomer, or prodrug of claim 7 is excluded or
the compound, salt, tautomer, or prodrug of claim 8 is excluded or
the compound, salt, tautomer, or prodrug of claim 9 is excluded or
the compound, salt, tautomer, or prodrug of claim 10 is excluded or
the compound, salt, tautomer, or prodrug of claim 11 is excluded or
the compound, salt, tautomer, or prodrug of claim 12 is excluded or
the compound, salt, tautomer, or prodrug of claim 13 is excluded or
the compound, salt, tautomer, or prodrug of claim 14 is excluded or
the compound, salt, tautomer, or prodrug of claim 15 is excluded or
the compound, salt, tautomer, or prodrug of claim 16 is excluded or
the compound, salt, tautomer, or prodrug of claim 17 is excluded or
the compound, salt, tautomer, or prodrug of claim 18 is excluded or
the compound, salt, tautomer, or prodrug of claim 19 is excluded or
the compound, salt, tautomer, or prodrug of claim 20 is excluded or
the compound, salt, tautomer, or prodrug of claim 21 is excluded or
the compound, salt, tautomer, or prodrug of claim 22 is excluded or
the compound, salt, tautomer, or prodrug of claim 23 is excluded or
the compound, salt, tautomer, or prodrug of claim 24 is excluded or
the compound, salt, tautomer, or prodrug of claim 25 is excluded or
the compound, salt, tautomer, or prodrug of claim 26 is excluded or
the compound, salt, tautomer, or prodrug of claim 27 is excluded or
the compound, salt, tautomer, or prodrug of claim 28 is excluded or
the compound, salt, tautomer, or prodrug of claim 29 is excluded or
the compound, salt, tautomer, or prodrug of claim 30 is excluded.

31. A method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of claims 1-30.

32. The method of claim 31, wherein said protein kinase is selected from the group consisting of VEGF receptors and PDGF receptors.